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DIFFERENTIATION OF THE DISEASES INCLUDED UNDER CHRONIC ARTHRITIS.[1]

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Conceptions in internal medicine have in recent years been evolving with unprecedented rapidity. The organization of medical research, the growth of the sciences fundamental to medicine, and the application of physical, chemical, and biological methods to the solution of the problems of physiology and pathology are so widening our knowledge of disease-processes that we are constantly being driven to readjustments, especially in our classifications of disease. Conditions formerly thought to be simple turn out on more exact study to be very complex, and, in turn, a new discovery may prove that conditions hitherto apparently disparate, are, in reality, united by a common bond. Thus, in some instances, our forerunners stand convicted of excessive simplicity of view; in others, of interpretations which were unnecessarily complicated.

The greater the definiteness with which we perceive and deal with our problems, the more steady and satisfactory is the progress toward their solution. Our newer conceptions of the infectious diseases illustrate the point well. Recently, attention has been turned again to the diseases of the individual organs with the hope of diminishing their vagueness. That this has not been without success, the newer studies of the cardiopathies and the nephro-

[1] Read, as one of two Reports on the subject, before the Section on Medicine of the International Medical Congress, London, August, 9, 1913; the other Report made by Professor Fr. v. Müller, of Munich, is to be published in Volkmann's klinische Beiträge.

pathies attest. And when we turn to the diseases of the joints (or arthropathies), including the diseases comprised under "chronic arthritis," the subject with which this report[2] is to deal, it is gratifying to find that, out of apparent chaos, definite forms are emerging; the discouragement felt at the utter confusion which formerly prevailed is giving way to hopefulness as well-characterized clinical syndromes appear, as anatomical changes revealed by the *x*-rays, at operation or at autopsy, assume distinct shape, and, especially, as etiological studies yield us patterns upon which positive conceptions of pathogenesis can be moulded. But despite the real progress which has been made, it must be confessed that the arthropathies are still veiled in deplorable obscurity. No one who reviews the bibliography of our own time can ignore it. And, as we shall see, the dimness, while due chiefly to our inability as yet, except in certain instances, to look at the processes from an etiological viewpoint, is to some extent dependent upon an intervening dust-cloud of terminology. In no part of medicine, perhaps, have *names* been used less satisfactorily than in designating the arthropathies; we find, on the one hand, one malady masquerading under many different names, or, on the other hand, one name used ambiguously, meaning sometimes one disease, sometimes another, or sometimes a group of separable diseases. Even today there are scarcely two authors in one country who use precisely the same terminology for the arthropathies; add to this the varying use of terms by writers of different nationalities and the lack of uniformity of expression becomes very perplexing. Notwithstanding, however, all the confusion which exists regarding names, a study of their history will reveal the fact that the introduction of each corresponded to some special conception, and that, for the purpose for which it was chosen, it usually served a useful function. The difficulties which have arisen have been largely due to the attempts made to force classifications and names made for different purposes into coincidence with one another. Ignoring the original purpose of a name, writers not infrequently use it for a wholly different purpose, with subsequent disorder and excitation of controversy. A comparison of the cases of joint diseases with which one is familiar in America with the cases described by writers in Great Britain, Germany, Austria, and France makes it clear that the material in different countries is not dissimilar. In an International Medical Congress like this it would seem fitting thoroughly to discuss the types now everywhere known, and to try to come to a general agreement as to the terms which may best be employed in describing them.

[2] This report is based upon (1) personal experience with the arthropathies in the medical clinic of the Johns Hopkins Hospital (1905–12); (2) a study of the bibliography; and (3) many consultations with my colleagues in the medical, surgical, and radiographic departments of the hospital.

To understand the origin of the many names now used for the various diseases included under "chronic arthritis," some acquaintance with the development of our knowledge of diseases of the joints, both acute and chronic, is indispensable. The diseases are not new. Bones, thousands of years old, have been found in Egypt which show unmistakable signs of deforming pathological processes in the joints (Page May). The ancient authors (*cf.* Scribonius Largus, A.D. 41)[3] used the term ἀρθρῖτις for acute diseases of the joints (like acute rheumatic fever), and the term ποδάγρα for gout; they seem also to have been familiar with chronic joint diseases other than gout. The term *rheumatism* (Lat. *rheumatismus* = Greek ῥευματισμός) meant liability to "rheum" and dates back to times when physicians believed that harmful phlegm flowed down from the brain and injured other organs of the body, a part of the humoral pathology which had adherents until the latter half of the seventeenth century; "rheumatism" seems to have been used, at first, as a name for some of the complications of gout. At the end of the sixteenth century, G. D. Baillou, a contemporary of Rabelais, reversed the ancient usage of the word *arthritis*, applying it to the gouty affections, and the word *rheumatism* to the acute diseases of joints. As early as 1683, Sydenham distinguished "chronic rheumatism" (rheumatism not accompanied by fever) from "gout," asserting that they are essentially different diseases.[4]

In the year 1800, in a Paris Thesis, Landré-Beauvais separated from true gout a condition to which he gave the name "primary asthenic gout" (*goutte asthénique primitive*), stating that it affects chiefly females, has a chronic course, and leads to enlargement and deformity of the joints, without tophi. The same disease was recognized by William Heberden, the elder (1710–1801), and carefully described by him in his famous *Commentaries;* at the same time he described as *digitorum nodi* the nodes (which bear his name) on the distal joints of the fingers. Just a little later (1805) appeared the memoir by John Haygarth, entitled *A Clinical History of Diseases*, part first being (1) A Clinical History of the Acute Rheumatism, (2) A Clinical History of the Nodosity of the Joints. In the first half of the nineteenth century, the French writers referred to the chronic non-suppurative joint diseases as "gouty rheumatism" (*rhumatisme goutteux*), and as "dry arthritis" (*arthrite sèche*); at about the middle of the century the terms "rheumatic gout" (Fuller, 1852) and "chronic rheumatic arthritis" (Adams, 1857) attained to considerable vogue in Great Britain. Soon after this, three names began to be employed which were

[3] Cited by Pribram in his admirable article in Nothnagel's System.

[4] That an attempt to make classifications more elaborate than the facts justify is not a failing peculiar to our times is shown by the fifteen varieties of chronic rheumatism described by de Sauvage and the thirty-four varieties differentiated by Cullen.

destined to play an important role in the terminology: (1) "primary progressive chronic articular rheumatism" (Charcot, 1853; Vidal, 1855), (2) "rheumatoid arthritis" (Garrod, 1859), and (3) "arthritis deformans" (Virchow, 1869). The first of the three names indicated the growing tendency to distinguish among the chronic non-gouty diseases of the joints a form that is primary (that is, chronic from the beginning), and a form that is secondary (that is, a chronic following an acute process); and the last of these three names referred to the marked changes in the bones and cartilages found at autopsy in certain cases of chronic joint disease. Virchow used "arthritis deformans" in an anatomical sense; it has since been used also in a clinical sense, but unfortunately in various ways. The adjective "deformans" is ambiguous, some authors having deformities of bones in mind (osteoarthritis deformans), others thinking instead of the pathological "deviations" due to contractures or other causes. In Germany the surgeons (R. von Volkmann, Schuchardt, Hoffa), and some internists (Schüller, Přibram, W. His), have distinguished sharply, as "arthritis deformans" or "osteoarthritis deformans," a disease monoarticular or oligoarticular in type, coming on slowly, usually in advanced life, never leading to true ankylosis, and presenting anatomically (and in *x*-ray pictures) extensive exostoses, especially at the edges of the articular cartilages; they do not include under "arthritis deformans" the other non-gouty joint-diseases, but group many of the latter together as "chronic articular rheumatism" (*chronischer Gelenkrheumatismus*), in turn subdivided into several groups (*vide infra*) and including the "primary chronic progressive polyarthritis" (*polyarthritis chronica progressiva primitiva* [His. A. Hoffa]). Some German writers, especially internists like Curschmann and Bäumler, have opposed the sharp separation of "arthritis deformans" from "primary progressive polyarthritis;" they include both under terms like "polyarthritis chronica deformans."

In America, Goldthwaite (1904), whose conceptions of the arthropathies have strongly influenced American workers, discarded the term "arthritis deformans," and, in addition to "chronic infectious arthritis," used the terms "hypertrophic osteoarthritis" (= "osteoarthritis deformans") and "atrophic arthritis" (= "primary progressive chronic polyarthritis"). These names have been extensively used by Painter, Osgood, Baer, and Fayerweather. Nathan (1906) uses a similar terminology, but extends it considerably in an effort to value clinically the results of studies in pathological anatomy. T. McCrae, in his exhaustive analysis in Osler's *Modern Medicine* (1909), uses the term "arthritis deformans" to include only cases of chronic arthritic change in which no definite etiological factor can be found, but he subdivides this great group into three main sub-groups, of which the first or "peri-

articular form" and the second or "atrophic form" appear to correspond (in part at least) to the "primary chronic progressive polyarthritis" above mentioned, while his third or "hypertrophic form" corresponds to the "osteoarthritis deformans" described above.

In Great Britain, the terminology used can be found in the excellent treatises of Sir A. B. Garrod (1876), A. E. Garrod (1890) Bannatyne (1896), Spender (1897), and Hale White (1902). Recently, A. E. Garrod (1910), in Albutt and Rolleston's *System*, has sharply distinguished (1) "osteoarthritis" (= "osteoarthritis deformans") from (2) "rheumatoid arthritis" (= "primary chronic progressive polyarthritis") and from (3) the "articular lesions of infectious diseases." The whole subject of the chronic arthropathies is being further illuminated in England through the investigations of the Committee for the Study of Special Diseases at Cambridge; the reports of Strangeways and Nicholson and their associates in the *Bulletins* of the Committee are a mine of information for all who are interested in chronic arthritis.

In France, Lancereaux (1888) used "chronic rheumatism" or "herpetism" as a general term, subdividing it into (*a*) "generalized chronic articular rheumatism" (= primary chronic progressive polyarthritis + chronic arthropathies secondary to acute processes) and (*b*) "partial chronic rheumatic arthritis" (= osteoarthritis deformans), including a form with effusion and a dry form; this classification closely resembles Charcot's (1889) subdivision into (*a*) "chronic progressive articular rheumatism" and (*b*) "chronic partial rheumatism." Pierre Marie (1896) used the terms (*a*) *rhumatisme chronique déformant arthrique ou diathésique* (= (in part) osteoarthritis deformans) and (*b*) *rhumatisme chronique déformant infectieux* (chronic arthritis following infectious processes). In the latter group he appears to include the cases of "primary chronic progressive polyarthritis." In 1896 Chauffard and Ramon also emphasized the conception of "chronic infectious arthritis" (= *rhumatisme chronique infectieux*), and in the same year Barbazon used the name "pernicious arthritis." Tessier and Roque (1897), under "chronic deforming rheumatism" (*rhumatisme chronique déformant*), include both *rhumatisme chronique progressif* (= primary chronic progressive polyarthritis) and *rhumatisme chronique partiel* (= osteoarthritis deformans).

Doubtless a familiarity with Italian and Russian literature, which, unfortunately, I do not possess, would reveal corresponding similarities and discrepancies.[5] Everywhere clinicians are obviously dealing with identical forms; to recognize them one has only to study the accounts of the cases, taking care not to be confused by the *names* attached to them.

[5] The review of the subject by Predtetschensky (1902) indicates that in Russia the same problems have to be met by clinicians.

Gradual Restriction of Meaning of the Terms "Gout," "Arthritis," "Rheumatism," and "Arthritis Deformans."

The brief historical notes given above indicate in a broad way the gradual alteration which, in the progress from vagueness toward definiteness, some of the conceptions and terms bearing upon joint diseases have undergone. At present, there is a still greater tendency to restriction and precision. In the minds of the laity the ideas which prevail are, it is true, still very hazy, "rheumatism" on the whole meaning to the man in the street something rather mild, "arthritis" something more severe, " gout" something reprehensible; but in the minds of medical men the same terms are attaining to more exact definition as the distinctions among joint diseases are becoming more clearly drawn on the ground of essential differences. As is always the case, however, where distinctions are not yet wholly firm and clear, it is difficult to know just how much those which we try to make are worth. Scientific men have had so many lessons in the unsatisfactoriness of "hard-and-fast distinctions" that they are prone to be shy in adopting them; they have so often had difficulty with the exceptional and puzzling cases which occupy a region intermediate between two opposed classes that they are skeptical when attempts at rigid definition are made. Still, all will grant that, to overcome ambiguity and vagueness, we must make use of classification, involving distinctions and definitions. And, moreover, no small part of our progress in medicine depends upon the disputes which arise between opposing parties as to the value of the distinctions made. One side may see only the value of a distinction and be blind to its defects; the other side may think the difference on which the distinction is made between two classes unimportant, asserting that, on the contrary, the resemblance is essential. We have a good example of this in the discussions which have arisen regarding the term "arthritis deformans;" they are resulting gradually in the use of distinctions which prevent certain important confusions into which we formerly fell.

The history of the arthropathies is as convincing as anything can be that the value of a given classification changes with circumstances as well as with times. Thus, the distinctions made at the period when Thomas Sydenham or Sir Benjamin Brodie worked, though most useful then, are obviously insufficient now. Furthermore, the distinctions which, today, the morbid anatomist needs, and which suffice for his purposes, may be very different from those necessary for, or sufficient for, the clinician in his work, or the etiologist in his studies. The *purpose* of a given name, or a given classification, should always be definitely understood. In medicine we have, at all times, to work in a world of rough distinctions, and medical men, perhaps more than most, have ever to be on

guard against the fallacies into which, through the imperfections of their distinctions, they may be misled. The importance of such considerations for an understanding of the difficulties of terminology which beset the study of the arthropathies, will, I trust, be sufficient excuse for the digression just made.

We may now turn to the tendencies at present noticeable in defining the terms "gout," "arthritis," and "rheumatism." There seems to be, at present, general agreement that the word "gout" shall be applied only to processes dependent upon abnormalities of the metabolism of purins. In the "gouty" arthropathy (*A. urica*) there is an excess of uric acid in the blood and a tendency to tophaceous deposits in the tissues. The accompanying clinical phenomena in "typical" gout are so characteristic as to permit of easy recognition, though in "atypical" cases there may be great difficulty in distinguishing gout from other diseases. At present, the tendency to avoid the use of the words "gout," and "goutiness" in describing diseases in which we have no evidence of abnormal purin metabolism seems to be universal; this accounts for the general abandonment of terms like "primary asthenic gout," "rheumatic gout," and "gouty rheumatism."

There is much more disagreement as to the use of the word "arthritis." Originally used in the sense of "acute joint-disease," it came in the sixteenth century to be limited rather to gout. In modern times it has been used almost in the general sense of "joint-disease" or "arthropathy," though a tendency, without good reason, to separate acute rheumatic fever and, to a certain extent, gout from the designation "arthritis" has been noticeable. If I judge the present tendency aright, it is to apply the term "arthritis" (and to limit it) to true inflammation of the joints in the sense of the pathological anatomists, that is, to all inflammatory arthropathies, acute and chronic, including (1) the arthritis of acute rheumatic fever and of other infections, and (2) all forms of chronic joint inflammation (including the gouty), but excluding the non-inflammatory arthropathies (for example, the purely degenerative).

More confusing still are the uses made of the words "rheumatism" and "rheumatic." Though most often employed in naming joint diseases, they have also been applied to diseases of other parts (muscles, serous membranes, eyes, throat, brain, nerves, etc.), diseases presumably due to the same causes as those producing the joint-diseases so named.

We have seen how "rheumatism" was first used to name diseases resulting from the flow of phlegm from the brain, how "rheumatism" and "gout" were first sharply distinguished by Baillou (1538–1616), how the non-gouty joint-diseases were divided into "acute rheumatism" and "chronic rheumatism" by Sydenham (1624–89), and how "chronic rheumatism" began to be divided into a "primary form" (chronic from the first), and a "secondary form" (following the "acute") by various writers, beginning with Landré-Beauvais (1800) and made clearer later by Heberden,

Haygarth, Charcot, Vidal, Jaccoud, and others. In order to understand current tendencies in defining "chronic rheumatism," the changes of fortune undergone by the term "acute rheumatism" must first be glanced at. For a long time "acute rheumatism" appears to have meant simply any acute arthropathy not traumatic or gouty in its origin. But gradually it has come to mean an acute febrile polyarticular affection, frequently complicated by endocarditis, pericarditis, or chorea, not leading to suppuration of the joint, but responding promptly to treatment with salicylates, and ending in recovery without residual joint change. It is interesting on examining the texts of Sir B. Brodie (1818), A. Bonnet (1845), E. Gurlt (1853), and R. von Volkmann (1882), to find how skilfully, before the advent of modern bacteriological studies, clinicians were able to separate acute articular rheumatism (*rhumatisme articulaire aigu, akuter Gelenkrheumatismus*) not only from (1) the pyæmic joint affections, but also from (2) gonorrheal rheumatism (*Rheumatismus urethralis; Tripperrheumatismus; arthromeningitis gonorrhoica*)[6] and (3) the polyarthritides complicating the acute exanthems, typhoid, dysentery, mumps, syphilis, etc. Hence it does not surprise us that when, after bacteriological studies, acute infectious arthritis came to be better understood, the acute non-suppurative, polyarticular joint-diseases resembling acute rheumatic fever, but differing from it in several important particulars (cause, course, occasional suppuration, relative inefficacy of salicylates), began to be grouped together as "pseudorheumatisms" (Bouchard) or as "rheumatoids" (Gerhardt). When the bacteria causing a given pseudorheumatism could be determined, a corresponding special name was applied (for example, Polyarthritis gonococcica, P. streptococcica, P. staphylococcica, P. pneumococcica). With the rise of this doctrine of the "pseudorheumatisms," the question again arose as to the existence after all of a true "acute articular rheumatism" in the narrower sense. Thus it was asked, Does not the whole series of pseudorheumatisms, taken together, account for everything known as "acute rheumatism?" Today no one longer questions the independence of "acute rheumatic fever" (*polyarthritis rheumatica acuta*) though its etiology is still entirely unknown.[7] Still, it is looked upon as a definite

[6] This was described carefully by Musgrave as early as 1723.

[7] A number of bacteria have been described as the cause of acute rheumatic fever (Mantle, Sahli, Poynton and Paine), but the majority of investigators have had negative results from cultures made from the blood and joints. In the medical clinic of the Johns Hopkins Hospital a large number of blood cultures have been made in acute rheumatic fever (true) by competent bacteriologists (R. I. Cole, B. Cohoe, F. J. Sladen, P. W. Clough, C. G. Guthrie, C. R. Austrian, R. Major, and T. P. Sprunt) with uniformly negative results. Very recently, E. C. Rosenow, of Chicago, has been able by use of an ascites-dextrose-agar medium to obtain bacterial growths (micrococci; diplococci; streptococci) from a majority of cases of "acute rheumatic fever;" the bacteria will not, at first, grow under either strictly aërobic or strictly anaërobic conditions but require a "partial oxygen pressure." It will be interesting to compare Rosenow's findings with those of Poynton and Paine: if it should turn out that the bacterial origin of acute rheumatic fever is demonstrable, a most important step forward will have been made.

infectious disease, probably depending upon a primary infection in the throat with secondary invasion of the blood with the virus (virus-æmia) and metastatic joint involvement.

The tendency at present is to limit the use of the terms "rheumatism" and "rheumatic" to diseases due to this unknown virus which causes "acute rheumatic fever." This is why, today, the term "chronic rheumatism" is, perhaps, best reserved for a chronic arthropathy due to the virus which causes acute rheumatic fever. There may be some reason, as T. McCrae has emphasized, to doubt the existence of such a chronic arthropathy; some of the evidence available is rather against it, though a number of the best authorities on diseases of the joints believe that it does exist, and the matter is best considered as yet unsettled. It can scarcely be definitely decided until the etiological agent in acute rheumatic fever is determined and it is found out whether this is present or absent in the cases of supposed "chronic rheumatic arthritis."

Differentiation of the Chronic Arthropathies According to the Pathological Anatomical Changes Met with in the Joints.[8]

If we now examine the attempts to classify the chronic arthropathies based upon pathological anatomical changes in the joints, we find that investigators have made their divisions according to two main principles:

1. The principle of considering the part of the joint involved (*site of the lesion*), and
2. The principle of considering the kind of morbid anatomical process concerned (*nature of the lesion*).

(*ad* 1) Thus according to the first principle, pathologists in coining names have classified joint diseases as follows:

(*a*) Those involving a joint as a whole (for example, *panarthritis*).

(*b*) Those involving predominantly the soft parts about a joint (for example, *periarthritis, periarticulitis, arthromeningitis externa*).

(*c*) Those involving predominantly the synovial membrane and its villi (for example, *synovitis* [*arthromeningitis*] *interna, arthritis villosa*).

(*d*) Those involving predominantly the cartilages and bones of a joint (for example, *arthritis deformans* (Virchow); *osteoarthritis deformans*).

[8] Excellent accounts of the anatomical changes can be found in the articles by Nichols in Keen's System of Surgery, Nicholson in the Cambridge report, Ziegler in his text-book, Schmidt in Aschoff's text-book, and Cornil and Ranvier in their *Histologie pathologique*.

An interesting example of the application of this first principle is discernible in the early descriptions of the chronic joint-diseases now known to be due to tuberculosis. The older authors separated them, according to the site of the lesion, into (1) those beginning in the soft parts (synovialis and periarticular tissues) and (2) those beginning in the ends of the bones entering into the formation of the joints. They called the former "white swelling" (*tumor albus*), and the latter "caries" (*arthrocace*). Billroth, thinking this distinction artificial, grouped both varieties under the term "fungous arthritis."

The sequels of joint-diseases have also been classified, in part at least, according to the site of the anatomical change; thus the distinction made between "true ankylosis" (*ankylosis vera*) and "false ankylosis" (*ankylosis spuria*) depends upon whether there is a union of the joint-surfaces themselves, as in the former instance (*ankylosis intracapsularis*), or, as in the latter, there is rigidity of the capsule (*ankylosis capsularis*), or of the periarticular soft parts (*ankylosis extracapsularis*).

(*ad* 2) Again, according to the second principle above mentioned, we might classify the chronic joint-diseases as follows:

(*a*) Those depending upon abnormal processes in development—the "malformations" or "teratological arthropathies" (*A. teratologica; A. congenitalis*).

(*b*) Those depending upon degenerative or metabolic processes (*A. chronica degenerativa; A. metabolica*), including, perhaps, (1) the atrophic arthropathies seen in tabes (*A. tabidorum*) and syringomyelia, and
(2) the tophaceous deposits of gout (*A. urica*).

(*c*) Those due to abnormal processes of circulatory or vasomotor origin (*A. chronica circulatoria*), including atherosclerotic arthropathies, the hemophilic arthropathies, and hydrops intermittens.

(*d*) Those dependent upon defensive and reparative processes, viz., the chronic inflammatory arthropathies (*A. chronica inflammatoria*), including, in the sense of Lubarsch.

(*da*) The chronic alterative inflammations (*Arthritis chronica alterativa*) in which regressive changes predominate, though with them are associated less marked exudative and productive processes. Here would be included the "atrophic arthritis" of Goldthwaite and of Nathan.

(*db*) The chronic exudative inflammations (*Arthritis chronica exudativa*), including the round-celled infiltrations and the chronic purulent and ulcerative processes in the joints (gonorrhea, tuberculosis, etc.). Here would be classed also many cases of arthritis following the other infections, and, probably, also many of the cases described

as "rheumatoid arthritis," as "primary progressive polyarthritis," or as "arthritis nodosa" (Schuchardt) in their *early* stages (when there is effusion or periarticular swelling).

(*dc*) The chronic productive inflammations (*arthritis chronica productiva*) in which proliferative changes in the fibrous tissues, cartilage, or bone predominate. The process may represent (1) an end-stage of an acute or subacute arthritis, or of an exudative arthritis of insidious onset, slowly progressing, (2) an arthritis which has been "dry" and "productive" from the beginning (*arthritis sicca* = *arthrite sèche* of French writers), or (3) a so-called "specific inflammation "or" infectious granulomatous change." Under chronic productive arthritis two main anatomical groups may be distinguished, according as (*i*) the joint-capsules or (*ii*) the bones and cartilages are the site of the principal productive changes. When the productive inflammation affects chiefly (*i*) the joint capsules, it often leads to either shrinking or to relaxation of these capsules; the bones become rarefied and softened; and the cartilages undergo absorption. If along with these changes the cartilages and the bones show no marked tendency to proliferation, we have the condition so often observed in cases of "primary chronic progressive polyarthritis" (= *Polyarthritis destruens* of A. Hoffa); owing to the softening of the bones, they easily undergo plastic distortion from the pressure exerted on them by shortening capsules or by muscular contractions; the ends of the bones flatten out; if they can deviate sidewise, they do so, giving rise to characteristic subluxations; when lateral deviation is prevented by the ligamentous structures, as at the carpus, the bones are squeezed into one another, undergoing the change so graphically described by the Boston school of orthopedists as "telescoping of the bones," with shortening of the parts in the proximodistal diameter. When the finger-joints are affected, the shortening of the proximal or middle phalanges by this telescoping process may be very striking, especially in the *x*-ray plates. The fibrosis and shrinking of the capsules in the disease just described put it anatomically in the larger group known as "adhesive or ankylosing arthritis" (*A. chronica adhesiva; A. chronica ankylopoietica* (Ziegler). But by this term is usually meant a chronic productive inflammation, which leads not only to pericapsular fibrosis and to fibrosis of the synovial layer of the joint-capsule with partial or complete obliteration of the recesses of the joint-cavity, but also to

pannus-formation on the articular surfaces, followed by complete fibrous or bony union of the opposing surfaces (*ankylosis fibrosa; ankylosis ossea*). This anatomical type includes many of the chronic ankylosing inflammations of the joints which follow infections, among other forms, the so-called "rheumatismus fibrosus (Jaccoud), and the kind of "poker-spine" known as "ankylosing spondylitis" (*spondylitis ankylopoietica*), in which there is true ankylosis of the joint-surfaces of the articular processes of the vertebræ and of the costovertebral articulations, along with ossification of the longitudinal ligaments of the spine. When the productive inflammation affects predominantly (*ii*) the bones and cartilages, the result is a "deforming arthritis" (*arthritis deformans*) with exostoses, osteoporosis, osteosclerosis, fibrillation, and atrophy of cartilage, ecchondroses, sometimes combined with villous proliferation, "lipoma arborescens," etc. Such changes may occasionally be met with as the end-stage of an alterative or of an exudative inflammation of long standing (= "secondary arthritis deformans"), but they seem to appear much more often, and more characteristically, as a process *sui generis*, productive from the first, with marked lipping of bones at the edge of the articular surfaces (= *primary arthritis deformans* = *osteoarthritis deformans* = *hypertrophic osteoarthritis*). The "primary osteoarthritis deformans "may involve more than one joint, though even then it appears usually as an oligoarticular affection rather than as a general involvement of the joints. As subvarieties of it may be mentioned (1) "hypertrophic osteoarthritis of the spine" (*spondylitis deformans*), and (2) "senile osteoarthritis of the hip-joint" (*malum coxæ senile*), a monoarticular affection in which erosions of cartilage with exposure of bone are marked, hence sometimes called "dry ulcerative arthritis" (*arthritis ulcerosa sicca*); in this malady there is often less periostitic proliferation than in other forms of osteoarthritis. It is in the various types of deforming arthritis, especially, that "free bodies" (*corpora libera articulorum*) (*of the hard variety*) are prone to be found (*Gelenkmause* of the Germans; *corps étrangers* of the French). In the third group of the chronic productive inflammations of the joints may be placed (*iii*) the so-called "specific" chronic inflammations or "infectious granulomatous" inflammations of the joints (*arthritis chronica granulomatosa*), including the different forms of tuberculosis, syphilis, leprosy, actinomycosis, etc., of the joints, differentiable in part on morbid anatomical

changes (tubercle, gumma), but more easily when their causes are studied. In this group, particularly, the necessity of helping out anatomical classifications by distinctions based upon etiology was relatively early found to be pressing.

(*e*) The chronic diseases of joints due to true tumor growth (*arthropathia neoplastica*) are rare. Primary sarcomas and endochondromas occasionally occur, but they are far less common than the proliferative and metaplastic processes of *arthritis deformans*, simulating (and often erroneously designated as) fibroma, enchondroma, or osteoma.

Differentiation of the Chronic Arthropathies According to the Etiological Factors Known, or Presumed, to be Concerned.

While conceptions based on pathological-anatomical changes have perhaps been dominant in the origin of names for the joint-diseases, we can also make out all through the terminology of the arthropathies the influence of etiological conceptions.

Phenomena accompanying diseases of the joints depend upon the "abnormal" alterations in the substances and energies of the parts; they are the "reactions" of the "system" to the "stimuli" which reach it. The structural changes involved in such reactions form the basis of the pathological-anatomical classifications, while the abnormal conditions determining the constitution of the system, the abnormal stimuli reaching the system, and the routes followed in reaching it, form the basis of etiological classifications.

The arrangement of substances and energies in a "joint-system" at any given time depends upon (1) the germ-plasm from which the individual has been derived, and (2) the influences, internal and external, which have acted (from the time of fertilization) upon the particular portions of the germ-plasm from which the joint-system came. In any broad consideration, therefore, of the causes of joint-disease such as is required if a differentiation of disease on etiological grounds is contemplated, the two factors of *heredity* and *environment* (internal and external) would have to be analyzed. That, in the chronic arthropathies, heredity in some instances is largely responsible, environment in some, every one will grant; to bring conviction on this point we have only to point to the gouty and the hemophilic arthropathies on the one hand, and to the traumatic and the infectious arthropathies on the other.

Knowledge regarding disease processes is, however, far too limited as yet to permit us to say how much a given "reaction"

is due to factors of heredity, how much to factors of environment, or, again, how much is due to "internal" causes and how much to "external." The "external" causes are, it is true, much better understood than the "internal." What we call "exciting" causes are very often external, while "predisposing" causes may be internal or external or both. Further, when dealing with a special "organ-system," like a "joint-system," and using the terms "external" and "internal" causes, we have to keep clearly in mind the fact that such terms may refer to the "organ-system" by itself or to the whole organism of which the "organ-system" is but a part. This point becomes especially important when in a given instance of polyarticular disease we ask first, Why are the joints diseased at all? and second, Why are some joints involved and others not?

When diseases of joints are named according to conceptions of etiology, the names sometimes refer to the mode of access of the pathological stimulus to a joint-system, for example, injury from the outside (= *traumatic arthropathy*), injury through the blood (= *hematogenous arthropathy*), injury through the lymph channels (= *lymphogenous arthropathy*), injury through the nerve paths (= *neurogenous arthropathy*)[9]

But, sometimes, names based on etiological conceptions refer rather to the particular variety of injury, that is, to the especial form of abnormal stimulus concerned; thus *physical* stimuli are concerned in traumatic arthritis, and, presumably, in the so-called "static" joint diseases (*statische Gelenkerkrankungen* of Preiser), *chemical* stimuli in the "toxic" arthropathies (for example, *arthralgia saturnina*), and *biological* stimuli in the "infectious" arthropathies due to bacterial invasion of the joints (*arthritis infectiosa; rhumatisme chronique infectieux* of Chauffard and Ramon).

And, in the third place, names suggesting etiological conceptions may refer neither to the mode of access of the noxa to the joint (*exposition* of the joint-system), nor to the particular variety of noxa concerned, but rather to some more or less vague predisposing causal factor (*disposition* of the joint-system or of the organism as a whole). Thus a predisposing *age* (as in *malum coxæ senile*), or the predisposing conditions of *poverty*, involving a combination of under-nutrition, cold, moisture, and depressing psychic influences (as in *poor man's gout* and *arthritis pauperum*) may be reflected in the terminology.

To deal with all the etiological conceptions upon which differentiations of the chronic arthropathies are being based, would be

[9] Distinctions might, perhaps, be made among the "neurogenous arthropathies." It may be that some are due to influences injurious to the joints acting directly through nerve-fibres, and that others arise in individuals suffering from neuropathy (tabes, syringomyelia); in the latter, there is room for discussion as to whether the injurious influences reach the joint directly through the nerves (perverted trophic influence) or through direct physical influences from the outside (trauma) as a result of loss of protective centripetal influences (anæsthesias).

beyond the scope of this report, but two of the ideas merit especial comment, on account of their influence upon contemporary medical thought. I refer (1) to infection, and (2) to static influences.

The chronic arthropathies of infectious origin. Since septic processes have been carefully studied by bacteriological methods and their joint complications have been found to be toxic-infectious processes due to the arrival in the joint, by way of the blood-stream, of some of the bacteria causing the general sepsis, the idea of an infectious origin of arthropathies has proved to be an illuminating conception. By far the majority of acute, febrile, non-traumatic arthropathies are now believed to be infectious in nature. In many instances the bacteria have been grown in pure culture from the inflammatory exudate in the joint. As examples of bacteria thus found responsible, may be cited (1) the gonococcus (in *polyarthritis gonococcica* following gonorrheal infection of the urethra, or of the conjunctiva), (2) the pneumococcus (in *polyarthritis pneumococcica* complicating lobar pneumonia), (3) the streptococcus (in *polyarthritis streptococcica* complicating erysipelas, streptococcal angina, puerperal infection), (4) the staphylococcus (in *polyarthritis staphylococcica* as a part of general staphylococcus sepsis), and (5) the meningococcus (in *polyarthritis meningococcica* complicating epidemic cerebrospinal meningitis). Now, since these acute infectious (hematogenous) arthritides of definitely determined bacterial origin sometimes end neither in death nor in early recovery, but in a chronic process in the joints (for example, chronic gonococcal arthritis), the idea of an infectious origin for many of the chronic arthropathies has gained credence (Bannatyne, Charrin, Chauffard, Goldthwaite, Schüller). The notion was soon extended to various chronic arthropathies in which, despite the absence of demonstrated bacterial causation, the local processes in the joints and the state of the rest of the body (slight fever, slight leukocytosis, secondary anemia, enlargement of the lymph glands, slight foci of local infection elsewhere) make the assumption of a continuous (or occasionally recurring) bacteriemia of low grade with joint-deposition seem possible and plausible (Allchin, Baer, Cave, Goldthwaite). Under this heading come the severe forms of arthritis occurring in childhood (Still's disease).

At the present time, the term "infectious arthritis" is used in a very loose way. It has been made to refer to (1) the arthropathies in which bacteria have been actually demonstrated in the diseased joints, especially in the infectious granulomas (tuberculosis, lues, lepra) and in those complicating the septicemias, (2) the arthropathies which appear obviously as complications, or as sequels, of diseases believed to be infectious, no matter whether the causal agent is demonstrable in the joints or not (for example, acute rheumatism; arthritis after influenza), no matter whether the joint disease is supposed to be due to the same cause as the primary

disease or to a secondary invader[10] (for example, arthritis after dysentery), no matter whether the germ of the primary disease is known or not (for example, arthropathies associated with or following scarlet fever, mumps, etc.), and no matter whether the assumed toxic infectious process affects the joints directly, or indirectly through the mediation of trophic nerves (according to the views of some regarding so-called atrophic arthritis and primary chronic progressive polyarthritis). Obviously, here, vagueness passes the permissible and a judicious restriction of the term "infectious arthropathy" seems desirable. Whether we should, with the rigid restrictionists, limit its use to arthropathies in which bacteria are actually demonstrable in the joints, or should extend it to include the arthropathies which may reasonably be supposed to be due to local bacterial deposition, though such deposition cannot yet be demonstrated, is open to discussion. We do not hesitate to regard scarlet fever and measles as acute infectious diseases, though their microbic origin still awaits demonstration, and, personally, I cannot help feeling it legitimate to designate as "infectious" the arthropathies like those of acute rheumatic fever, and those chronic types growing directly out of acute or subacute processes associated with fever, leukocytosis, and enlarged lymph glands. But, pending further investigations, it does seem desirable when differentiating the arthropathies on etiological grounds, carefully to distinguish (1) the demonstrably infectious from (2) the probably infectious, (3) the possibly infectious, and (4) the certainly non-infectious. We should also, when using the term "infectious," keep clearly in mind the difference between (*a*) an infection in a joint-system itself, and (*b*) an infection somewhere in the organism as a whole, with secondary non-infectious changes (toxic, nutritive, trophic) in a joint-system. I emphasize this point because of the great importance, in the chronic arthropathies, of minute foci of infection distant from the joints and of their removal as a therapeutic measure. Chronic inflammations of the paranasal sinuses (including the antrum of Highmore), chronic tonsillitis, chronic otitis media, pyorrhea alveolaris, alveolar abscess, chronic bronchitis, chronic ulcerative enteritis, chronic appendicitis, cholecystitis, chronic pyelitis, chronic cystitis, chronic urethritis, spermatocystitis and prostatitis, chronic salpingitis, and chronic endometritis may be mentioned among the many possible foci whence influences injurious to the "joint-systems" of the body may emanate, and this without prejudice as to whether these influences are (1) metastatic infectious, (2) toxic, (3) neurotrophic, or (4) noxious in still other ways.

Much interest has been shown in the possibility of an infectious

[10] It would seem that many of the cases described as Poncet's disease (*rhumatisme tuberculeux*) are really instances of infectious arthritis of unknown origin occurring in individuals suffering from tuberculosis, rather than metastatic tuberculous infections of the joints.

origin for the so-called "primary chronic progressive polyarthritis" or "rheumatoid arthritis" of Garrod. The mode of onset in certain cases, the course, and the *x*-ray changes have made many believe that this terrible disease is due to a chronic infectious process involving joint after joint. Though bacteria have from time to time been described in the joints, the findings of the observers are discordant. If the malady be a specific infectious disease the future will have to determine the microörganism responsible, the portal or portals of entry into the blood, and the important predisposing factors. The possibility that this disease may be due sometimes to one microörganism, sometimes to another, must also be kept in mind. For, though the clinical and pathological changes are so uniform that they suggest a single specific cause, our experience with meningitis, pleuritis, etc., has taught us to await actual knowledge before attempting to close a discussion.

The chronic arthropathies of static origin (*Arthropathia chronica statica*). Recently a view has been advanced by Preiser according to which the "arthritis deformans," in the sense of the pathologists, in both its primary form and its secondary form (*vide supra*), is due to abnormal static conditions in the body. Applying Albert's law of the static unity of the lower extremity—"the pelvis, thigh, leg, and foot form a static unit"—and extending the conception also to the upper extremity, Preiser maintains that a disturbance of a static unit is felt not only locally, but, also, usually in all the joints belonging to the unit. In a rachitic genu valgum, for example, in addition to the displacement at the knee, the position of the head of the femur in the acetabulum is abnormal, and the apposition of the articular surfaces in the ankle-joint is disturbed; in other words, a "pathological incongruence" of the joint surfaces throughout the whole "static unit" results. A "pathological incongruence," while especially common as the result of rickets, may also follow the muscular weakness and softening of bones in other enfeebling diseases (influenza, visceroptosis), with change in the direction of a limb in its long axis, or, indeed, with rotation around any one of the three stereometric axes. In such states, the joint structures are more exposed to trauma and the nutrition of the joints may suffer from compression of the bloodvessels and nerves supplying them. Gradually the important changes of "arthritis deformans" appear in the form of fibrillation of the articular cartilages, degeneration, and proliferation of villi, marginal osteophytic outgrowths, and subchondral cyst-formation. While "arthritis deformans" is most often met with in advanced life, cases of "juvenile arthritis deformans" of the hip have been described; according to the view mentioned, they are looked upon as secondary arthritis deformans due to a "pathological incongruence" following the healing of an infectious (tuberculous) coxitis

in childhood. Those who support this static origin of chronic deforming osteoarthritis look upon the formation of osteophytes as an effort at compensation for the "incongruence" of the joint. They also see a support to the doctrine in the beneficial effects obtained from orthopedic measures directed toward the correction of flatfoot, genu varum, genu valgum, coxa vara, etc., in cases of deforming arthritis.

Differentiation of the Chronic Arthropathies According to the X-ray Findings.

Undoubtedly the greatest aid of relatively recent origin in the differentiation of the arthropathies during life is that yielded by radiographic examination. If good plates are made, not only is the condition of the bones and the cartilages clearly revealed, but much also can be learned concerning the state of the soft parts surrounding the joints, the synovial membrane with its villi, and the recesses of the joint-cavity.[11] A good radiograph is a veritable autopsy *in vivo* of a joint-system. We can decide at once as to the presence or absence of (1) periarticular swelling, (2) luxations or subluxations, (3) pathological deviations, (4) narrowing of joint slits, (5) atrophy or destruction of cartilage, (6) erosion of subchondral bone on the articular surface, (7) rarefaction or condensation of bone due to increase or diminution of lime-salts (also osteoporosis and osteosclerosis), (8) distortions of bone evidently due to softening and pressure, (9) tophi, (10) cysts, (11) osteophytes and exostoses, (12) subperiosteal swellings, (13) fibrous or bony ankyloses, (14) calcified free bodies, (15) calcification or ossification of ligaments, and (16) lime-deposits in bursæ. One of the most striking features often to be met with in *x*-ray plates is the evidence of so-called "acute bone atrophy" (Sudeck, Hale White, Kienbock, Exner). While a certain amount of rarefaction may result from inactivity or immobility, the very marked examples of "acute bone atrophy" are thought by some to be due to reflex trophic influences; others feel sure that even the marked examples are due to disuse (F. H. Baetjer) or to local toxic influences.

With the aid of Dr. F. H. Baetjer, the actinographer to the Johns Hopkins Hospital, I have recently studied carefully the *x*-ray plates derived from the arthropathic patients in the medical clinic and compared them with the clinical findings, as tabulated for me by Dr. Helen Watson. In this study we have been impressed by several points, most of all by the fact that the *x*-ray findings and classifications based thereon accord closely with those of

[11] The recesses of the joint-cavity are exquisitely revealed in *x*-ray plates made after injections of the joints with oxygen-gas. In the knee-joint, especially, if there be any doubt as to the differentiation between osteo-arthritis deformans and adhesive arthritis, examination by this method may be decisive.

pathological anatomy. *In the x-ray findings we have to deal entirely with form-relations and the inferences which can be derived therefrom.* It is not surprising, therefore, if in the terms "hypertrophic arthritis" and "atrophic arthritis" of the radiographers we meet again the "arthritis deformans" on the one hand, and on the other the "alterative arthritis," "adhesive arthritis," and "ankylopoietic arthritis" of the pathological anatomists.

Aside from gout, the neurogenic arthropathies, and possibly tuberculous and luetic arthritis, in which the *x*-ray plates are sometimes characteristic, the radiologist can rarely from the *x*-ray alone speak with any certainty as regards etiology. Again, as to predicting to which clinical group a given case belongs by inspection of the radiogram, the actinographer can often say that his "hypertrophic arthritis," with its non-obliterated joint-cavity, its condensation of bone, its large exostoses, and its marginal lipping, must belong clinically to (1) the benign osteo-arthritis deformans of advanced life (= primary *A. deformans*), to (2) an end-stage of an infectious or traumatic arthritis (= secondary arthritis deformans), or to (3) a neuropathic arthropathy; and he may suspect that his "atrophic arthritis" is clinically probably either (1) a primary chronic progressive polyarthritis (polyarthritis destruens) or (2) an arthritis secondary to some (other) infectious process. Further than this he is disinclined, and I think properly disinclined, to go. Finding how frequently disappearance of the joint slits, atrophy of cartilages, softening and distortion of bones with telescoping appear in the plates which he is told have come from patients suffering from "infectious arthritis," an actinographer's tendency may be to group all cases exhibiting these changes under the heading "infectious arthritis." This inference may turn out to be justifiable, though it is, as yet, hypothetical. For distinguishing, by *x*-ray examinations, the different kinds of infection (gonococcal, streptococcal, etc.), with the exception, perhaps, of the luetic and tuberculous types, adequate criteria are lacking. In an *x*-ray report, therefore, we should discriminate sharply between (1) the objective morphological findings reported, and (2) any interpretative impressions regarding probable etiology or probably clinical type. A report from an *x*-ray laboratory which gives merely a diagnosis couched in etiological terms may be very misleading to clinicians; in the team-work of a great hospital, therefore, the radiographers on making their reports should be encouraged to describe objectively the abnormal form-relations found, and to give only anatomical diagnoses; or, if they, through long experience in the correlation of *x*-ray findings with clinical phenomena, feel themselves justified in drawing clinical or etiological inferences, they will be most helpful if they will definitely designate the latter as such in an appendix to the actual *x*-ray report.

What has been said above refers to the *x*-ray study of the joints in general. But the actinographer and the clinician must be familiar with the *x*-ray findings peculiar to each joint-system. The technique of radiography is rapidly undergoing great improvement. The precise position of the parts at the time of exposure may be determining as to whether an abnormality present in the joint becomes visible, or not, in a plate. As examples may be mentioned (1) the difficulty of revealing slight bone changes in the shoulder-joint (P. Ewald, 1911), and (2) the difficulty (until Schlayer in 1906 showed how in the lumbar region to project the joint slits into the intervertebral spaces in the plate) of studying the changes in the joints between the articular processes of adjacent vertebræ in ankylosing spondylitis.

Reports on individual joints in the most different diseases are now available, but in a very scattered bibliography; it would be most helpful if we could have an epitome of this material brought together in a single volume.

The Principal Chronic Arthropathies Arranged in Clinical Groups.

Though many attempts have been made systematically to arrange the chronic arthropathies in clinical groups, none of them has proved wholly satisfactory or attained to universal acceptance. While clinical observation has taught us that certain well-defined types are met with over and over again, presenting such characteristic appearances and running such constant courses that they are deserving of treatment as separate clinical entities, when we are actually confronted by an individual case which deviates somewhat from the more "typical" forms, it may be extremely hard to place it, with entire satisfaction, in any one of the classes set up. Attempts at clinical classification are further complicated by the fact that one and the same clinical type has often been described under different names, and, worse still, and most systematic writers complain of it, each of these names may have been used also for other, wholly different, types. The failure of the terminologies based upon anatomical, etiological, and clinical conceptions to coincide with one another has been made, in the preceding sections of this report, sufficiently clear. The same difficulty of harmonizing classifications made for these three different purposes has been met with, often enough, in other domains, for example, in pneumonia, in osteomyelitis, in conjunctivitis, in angina. An agreement among these different modes of classification could only be expected, as Lubarsch has emphasized, if the course of the pathological phenomena depended exclusively on the factors starting the process, and if the organism were not able to react in different ways to the same stimulus. But since

the course and nature of disease are dependent upon many circumstances other than the external and internal stimuli concerned, and the cells possess only a limited number of modes of reaction, it is not possible that the clinical and anatomical phenomena of diseases can be satisfactorily rubricated on the basis of the different noxæ giving rise to them. In other words, we can never expect more than a partial coincidence of clinical, anatomical, and etiological groupings.

In modern clinical classifications, however, we feel justified in utilizing not only the anamnesis and the results of our general physical, chemical, and biological studies of the patient, but also (1) pathological-anatomical conceptions insofar as the *x*-ray findings and our physical examinations will permit us to value them, and (2) etiological conceptions insofar as they also can be valued through the anamnesis and through special chemical and bacteriological tests in given cases. The terminologies used for clinical purposes, therefore, are no longer based simply upon external appearances and the mere course of the disease, but must often reflect also anatomical and etiological considerations based upon a correlation of clinical experience with anatomical finding and demonstrated causal relationships. There can scarcely be objection to this as long as we clinically do not attempt to draw other than really justifiable anatomical and etiological inferences.

As a tentative classification of the principal diseases usually grouped under the designation chronic arthritis, the following rubrics would seem to be, at present, most useful:

I. The true gouty arthropathies (*A. chronica urica*).

II. The arthropathies of severe nervous disease (*A. tabidorum; A. syringomyelica*).

III. The (primary) hypertrophic osteoarthropathies (osteoarthritis hypertrophicans or osteoarthritis deformans), a relatively benign affection.[12]

IV. The secondary chronic arthropathies, following various infections (*A. luetica, A. tuberculosa, A. chronica gonorrhoica, A. chronica rheumatica,* if it exist, etc.), and those following small foci of infection (microorganisms often unknown) in various parts of the body.

V. The so-called (primary) chronic progressive polyarthritis—of all arthropathies the most malign.

In relation to the above five headings mention must be made of several special conditions; namely:

(*a*) The villous arthritis of Goldthwaite.

(*b*) The chronic arthropathies of the spine.

(*c*) Still's disease.

[12] This is not to be confused with the "osteoarthropathie hypertrophiante pneumique" of Marie or "pseudoacromegaly," in which there is slow thickening of the bone beneath the periosteum—the "toxigenic osteoperiostitis ossificans" of Sternberg.

(*d*) Heberden's nodes.
(*e*) Bouchard's comptodactylie.
(*f*) Subcutaneous fibroid nodules.

Confronted with a single case of chronic arthropathy it is often convenient to consider groups I to V above mentioned in serial sequence.

ad I. The *true chronic gouty arthropathy* is usually easy to recognize, at any rate in the typical cases. The heredity, the acute exacerbations, especially as nocturnal attacks, the presence of tophi, the sites of predilection, the increased amount of uric acid in the blood (Garrod, Magnus-Levy), and the deficient purin tolerance (method of v. Noorden and Schliep, 1905), suffice for the diagnosis. In atypical cases there may, however, be some difficulty in distinguishing the disease from atrophic or infectious forms of arthritis. The *x*-ray findings in a gouty joint are sometimes distinctive (spherical foci in the bone substance near the joint, or often in the form of a semicircular defect of the articular surface of a bone with sharp, punched-out margins; if such a lesion be present in a joint of one foot there is often a similar lesion in the same joint of the other foot).

ad II. The *neuropathic arthropathies* are easily ruled out if, in addition to the examination of the joints, a thorough neurological investigation be made (tests of sensibility, knee kicks, pupils, etc.). Moreover, the sudden onset, the marked enlargement of a single joint, and the absence of severe pain, are characteristic. Astounding changes are made visible by the *x*-rays; bizarre, monstrous hypertrophic lesions predominate; besides excrescences upon the bone and huge calcified free bodies, calcified masses are usually visible in the extra-capsular tissues; some regressive (atrophic or absorptive) changes are also present and there is usually extreme disintegration of the joint.

ad III. The (*primary*) *hypertrophic osteoarthropathy* (osteoarthritis [osteoarthropathia] hypertrophicans or deformans) is usually easily recognizable. Though most often met with in advanced life, the same or a similar malady may occur in youth, especially after slight trauma. One joint is chiefly affected, or several joints (usually only a few) may be involved. This mono-articular, or oligo-articular, distribution is in marked contrast with the more general polyarticular distribution of Groups IV and V. The large proximal joints of the extremities are most often involved (hips, shoulders, knees). There is an absence of the steady progression characteristic of Group V. Both sexes are affected, males predominatingly. The general health may be but little disturbed. The disease does not lead to true ankylosis, though the joint-

movements may be somewhat limited through interlocking of exostoses. On palpation, lipping of the bone at the edge of the cartilage may be sometimes made out. Free bodies are common. In radiograms, the joint-slits are often well preserved though the cartilage may be eroded, accounting for the grating which may be palpable on movement of the joint; the joint-slits do not entirely disappear, as in Group V and often in Group IV. As the joint-cavity is not obliterated, if oxygen be injected (method of Werndorff and Robinson) the capsule unfolds well, showing the absence of extensive adhesions and of shrinking. The presence of extensive osteophytic outgrowths, or of marked marginal lipping in the *x*-ray plates, especially when the clinical symptoms have been slight, is characteristic. Static disturbances, leading to pathological incongruence of the articular surfaces, and a history of trauma are common in these cases. The disease is often asymmetrical. Among the monoarticular forms, the so-called malum coxæ senile is included. One of the spinal arthropathies (spondylitis deformans) appears to belong in Group III (*vide infra*).

ad IV. In considering the possibility of a *chronic arthropathy secondary to some infectious process* it is well to think first of the chronic arthropathies due to infectious granulomatous processes (tuberculosis, lues, lepra, etc.). Here the white swelling (*tumor albus*) of Wiseman, a suppurating fistula, the anamnesis, the presence or absence of lesions elsewhere in the body due to the primary disease, the study of *x*-ray plates (destructive processes in tuberculosis, sub-periosteal swellings, regular or irregular in outline, in lues), the Wassermann reaction, and the tuberculin tests may help to clear up the diagnosis. After lues and tuberculosis have been excluded, the anamnesis may be gone into very carefully with reference to a history of a preceding acute infection, either of the joints themselves or of other parts of the body. One tries to determine whether or not the chronic arthropathy has followed a true acute articular rheumatism or one of the so-called acute infectious pseudo-rheumatisms (*vide supra*). It is clear from our examination of many of the cases recorded in the bibliography as "chronic rheumatic arthritis" following acute articular rheumatism, that the authors were in reality not dealing with a chronic arthritis following this affection (in the narrower sense) at all, but with a chronic arthritis following some one of the various other forms of acute infectious arthritis. Cultures from the blood, from the joint-fluid or from a regional lymph gland, complement-deviation tests, tests for bacteriolysins, agglutinins, etc., may occasionally be of help. This study may be followed by a systematic physical examination

in which the various possible primary foci of infection, mentioned in a preceding paragraph under infectious arthritis, are sought for. The search for intracellular Gram-negative diplococci in "milkings" from the prostate and urethra in the male, or from Bartholin's glands, the urethra, and the secretions from the cervix uteri in the female, and a thorough examination of the nose and of the paranasal sinuses, utilizing the methods of transillumination and of *x*-ray examination of the sinuses, should here form a part of the regular routine. The presence or absence of pyorrhea alveolaris, of antrum disease, of abscesses at the roots of the teeth (*x*-ray), of chronic tonsillar infection (palatine or pharyngeal), and of chronic otitis media, should be determined. If the case be seen in the later stages, a marked asymmetry of the joints affected, an absence of steady progression, or the complete ankylosis of single joints, may speak for Group IV rather than for Group V.

ad V. If the case does not clearly belong to one of the first four groups it is most important, from the standpoint of prognosis, to decide whether or not it really belongs to Group V, the so-called *primary chronic* (*progressive*) *polyarthritis*.[13]

Clinically, primary chronic progressive polyarthritis (Group V) may appear as either one of two sub-varieties. In both of these, the involvement is outspokenly polyarticular, the small distal joints of the fingers, toes, wrists, ankles, usually being involved first. Later, the knees and elbows may become involved; the hips and shoulders frequently escape. These small joints become involved symmetrically. The jaw joint and the sternoclavicular joint are not infrequently affected, and, curiously enough, usually asymmetrically. Some of the cases of ankylosing spondylitis (*vide infra*) belong to category V.

[13] The term "primary" in Group V and the term "secondary" in Group IV are used in a sense similar to the terms "primary" and "secondary" in connection with the anemias. We speak of a "primary anemia" when we mean an anemia of the Addisonian or Biermer type, not secondary to any well-known cause of anemia, though we realize that it must be secondary to some cause. Similarly, the "primary chronic polyarthritis" may not be obviously secondary to any acute primary infection elsewhere in the body. If it be an infectious disease, however, the bacteria or their toxines must reach the joints by way of the blood, and the bacteriemia and the polyarthritis are then "secondary" to some primary focus of infection. Until the etiology is determined definitely, however, there would seem to be no objection to the use of the word "primary" in this way. It seems likely that the word "primary" was applied to this disease in the first place in a different sense, meaning that the disease was chronic from the beginning (the *rhumatisme chronique d'emblée* of French writers); it seems now that it may, especially in childhood and adolescence, sometimes begin subacutely or even acutely with fever and sweat. The term "primary chronic progressive polyarthritis" is rather unwieldy on account of its length. There is much to be said in favor of A. E. Garrod's suggestion to use "rheumatoid arthritis" instead; the objection to this lies in the fact that "rheumatoid arthritis" has been used to comprise both this type and Group III, while Gerhardt referred to the infectious pseudo-rheumatisms preceding the chronic cases of Group IV as "rheumatoids." If there could be a general agreement to limit the term "rheumatoid" to V, the expression would be a convenient one for clinical use.

In one sub-variety (A) the disease may begin either insidiously or with an acute, or subacute, stage, with fever; in both forms of onset a striking feature is the periarticular swelling. Each joint of the proximal row of the joints of the fingers (with the exception of the thumb) often presents a spindle-shaped or fusiform appearance and feels elastic when compressed between the thumb and forefinger of the examiner. Most of the small joints in the distal parts of all four extremities may become affected in serial sequence. It is often impossible in the early stages to decide whether we are dealing with a true chronic progressive polyarthritis of Group V or with one of the serious maladies of Group IV.

In the second sub-variety (B), most often met with in women near the menopause, the onset may be very insidious. The patients complain first of formication, of chilly feelings, and of slight stiffness of the metacarpophalangeal and interphalangeal joints (except those of the thumb). Muscular atrophy quickly appears, especially of the interossei. Contractures gradually develop. The disease spreads to a large number of the more distal joints in all four extremities. The fingers become deflected ulnarward. The hands may present the "flexion-type" or the "extension-type" of Charcot, or the "straight" type, but these do not represent essential differences and are unimportant for classification. On *x*-ray examination the joint-slits are found to have disappeared, owing to atrophy of cartilage, the bones are softened, and may have undergone distortion or telescoping, and they are usually markedly atrophic—so-called "atrophic arthritis" of Goldthwaite (*vide supra*).

The sub-variety A is sometimes called the *exudative type;* it is the "periarticular type of arthritis deformans" (in part) of T. McCrae, and corresponds to the "nodosities" of Haygarth, the *rhumatisme noueux* of Trousseau, the "arthritis nodosa" of Schuchardt, and the "chronic infectious arthritis" (in part) of Goldthwaite.

The sub-variety B is the so-called *dry form,* and corresponds to the "atrophic arthritis" of Goldthwaite, the "atrophic type of arthritis deformans" of T. McCrae, and the *arthrite sèche* (in part) of French writers.

The sub-variety A can certainly be simulated by chronic gonorrheal polyarthritis; *x*-ray plates will not distinguish between them. In lues hereditaria tarda an arthropathy similar to sub-variety A is sometimes seen, but it should not be difficult to exclude it (Hutchinsonian teeth, keratitis, positive Wassermann, luetic changes in *x*-ray plate at epiphyseal line).

The absence of endocardial and pericardial changes in "primary chronic progressive polyarthritis" is striking when contrasted with the findings in acute rheumatic fever, the acute pseudo-rheumatisms, and in the chronic infectious arthritides.

It cannot be too strongly emphasized that sub-variety B is often (some think always) an end-stage of a condition beginning as sub-variety A. It ought to be acknowledged, too, that it is *possible* that later on Group V will not be considered separately as a disease *sui generis*, but will be placed in Group IV; in other words, it may be that the clinical appearances described as V may follow upon a variety of infections. For the present, the weight of evidence seems to me to favor the view that V is really an independent disease of unknown though unitary etiology (probably infectious).

A few words must now be said concerning the various special joint conditions mentioned above and their relation to the five main groups.

(*a*) *The Chronic Villous Arthritis of Goldthwaite.* This form of "dry joint" is believed by Goldthwaite not to be a general disease at all but a local process entirely, with no tendency to progression, characterized by an absence of general symptoms, by crepitation or creaking of the joint on motion, with varying degrees of pain and tenderness on movement. It is most commonly met with in the knee as the result of flatfoot. This type appears to be one of the "static arthropathies" of Preiser. It probably corresponds in Hoffa and Wollenberg's classification to "chronic irritative arthritis." It seems likely that it may follow the action of causes of different kinds.

(*b*) *The Arthropathies of the Spine.* The subject is difficult to deal with in a few words. The most important point to emphasize is, it seems to me, the fact that the joints and bones of the spine are subject to diseases precisely in the same way as the other joints of the body. We meet in the spine with (1) the gouty, (2) the neuropathic (tabetic), (3) the hypertrophic osteoarthritic, (4) the secondary chronic infectious, and (5) the primary chronic progressive forms. Anatomically, aside from traumas, the neuropathic arthropathies and the infectious arthritides of the spine (tuberculosis, lues, gonorrhea, typhoid, etc.), which usually affect the spine locally rather than throughout its whole extent, two main processes seem to occur in the vertebral column: (1) a hypertrophic osteoarthritis of the spine (*spondylitis deformans* and (2) a chronic ankylosing arthropathy of the spine (*spondylitis chronica ankylopoietica*).

In hypertrophic osteoarthritis of the spine (*spondylitis deformans*) the process seems to begin in the intervertebral disks; there are marked exostoses on the bodies of the vertebra and, especially, "lipping" of the vertebral bodies at the edge of the intervertebral disks, often with a few clasp-like formations extending from vertebra to vertebra, but never so extensively as in the ankylosing forms. The small joints between the articular processes never undergo intracapsular ankylosis in this disease, though

motion may be limited by exostoses. The nerve roots may be compressed. The disease occurs chiefly in advanced life. It almost never causes complete rigidity of the thorax.

In *spondylitis chronica ankylopoietica*, the disease begins in the small joints of the articular processes and quickly leads to ankylosis; the costovertebral articulations are often involved also. The ligaments of the spine sometimes become ossified, but many of the bony bridges or clasps uniting the vertebræ may be independent of the ligaments. Of this chronic ankylosing spondylitis, two clinical forms have been described: (1) the "Marie-Strümpell subtype" beginning below and extending upward, described by Marie as *spondylose rhizomélique*, on account of the simultaneous involvement of the articulations of the vertebral column and the proximal joints of the extremities (hips, houlders); and (2) the "Bechterew subtype" with outspoken kyphosis of the upper thoracic spine, the process beginning above and extending downward.[14] Later studies (Fraenkel, Simmonds, Janssen, Anschutz, Plesch) have shown that all sorts of transitions exist between the Bechterew type and the Strümpell-Marie type; these two subtypes do not represent anatomically separable processes in the spine. Rigidity of the spine is easily recognizable clinically. Pains in the spine, radiating into the trunk or the extremities, stiffness gradually extending to all movements of the spine, with a tendency to kyphosis, are characteristic phenomena.

The differential diagnosis between spondylitis deformans and the ankylosing variety is, in most cases, easily made. If the breathing be wholly abdominal owing to ankylosis of the costovertebral articulations or to the general approximation of the origin and insertion of the accessory respiratory muscles from kyphosis or from stiffness of midthoracic spine, or if the disease occur in young persons, under forty years, it is almost certainly chronic ankylosing spondylitis. The spine is more uniformly involved throughout its whole length in the ankylosing type than in spondylitis deformans. Radiograms are decisive in most cases. As to early cases, in spondylitis deformans the bone changes may be marked and the clinical symptoms slight, while in the ankylosing spondylitis severe clinical symptoms may precede demonstrable bone and joint changes by a year or longer.

(*c*) *Still's Disease.* This disease, a chronic arthritis of childhood, described by G. F. Still (1897), probably represents neither a clinical nor an etiological unity. In Still's disease we appear sometimes to deal with a secondary chronic infectious arthritis (Group IV) and sometimes with a primary chronic progressive polyarthritis (Group V). The presence of a large spleen, large

[14] A few of the cases described clinically as Bechterew's type turn out on *x*-ray examination to be spondylitis deformans.

lymph-glands, leukocytosis, and secondary anemia are strongly suggestive of chronic infection.

(*d*) *Heberden's Nodes.* These nodes are due to excrescences on the base of the terminal phalanges of the fingers. They are easily recognizable on inspection, on palpation, and in the *x*-ray. In my experience they occur most often in association with chronic hypertrophic osteoarthropathies, though they are sometimes seen in gout, and they sometimes occur as an isolated phenomenon, not associated with arthritis of the other joints. In the *x*-ray the adjacent joint may be but slightly affected, or, in some cases, the joint may show changes like those in primary chronic progressive polyarthritis. Heberden's nodes cannot, therefore, be said to be pathognomonic of any one form of chronic arthropathy; indeed they seem to occur in connection with several different forms, and by themselves. It would seem probable that Heberden's nodes do not represent even a morphological unity. They appear sometimes to be true exostoses (in hypertrophic osteoarthritis), sometimes to be projections due to softening and flattening of the base of the terminal phalanx (in infectious and in chronic progressive arthritis), and, finally, sometimes to be nodules due to gouty changes in the bones. Dr. W. S. Baer tells me that even on palpation varieties of Heberden's nodes are distinguishable; certainly in radiograms a variety of structures can be made out in the different types of cases.

(*e*) *Bouchard's Comptodactylie.* Bouchard has described fusiform swellings of the proximal finger-joints as an accompaniment of dilatation of the stomach; they are said to disappear when the stomach lesion is cured. Přibram has seen one such case. I have not observed this relationship. The relation of chronic arthritic affections to various disturbances of the digestive tract has been emphasized by Coutaret and also by Goldthwaite (in visceroptosis).

(*f*) *Subcutaneous Fibroid Nodules.* These little bodies attached to the tendons and fasciæ (Meynet, Barlow and Warner, T. B. Futcher, Hawthorne) may occur in almost any form of chronic arthritis. They were at one time supposed to be pathognomonic of true "rheumatic" affections. They are not to be confused with the *nodosités cutanées éphémères* of Fereol.

In bringing this report to a close I would reëmphasize certain points, namely: (1) The constant recurrence of well-characterized clinical types in the experience of observers in all countries; (2) the astonishing accuracy and vitality of the names that have been used for definite purposes; (3) the unfortunate confusion which has arisen largely through trying to use names introduced for a specific purpose for entirely different purposes, and especially through the efforts to make clinical, anatomical, and etiological classifications coincide; (4) the gratifying progress in differen-

tiation thus far made in a group of diseases formerly supposed to be one disease; and (5) the prospect of still more satisfactory differentiation to follow advances in etiological knowledge when they can be made. It is to be hoped that the discussion may go far toward clarifying our ideas of the chronic arthropathies; may it also spur us on to researches which will lead us, gradually, still further along the path out of vagueness toward definiteness!

SOME CAUSES OF DISAPPOINTMENT IN OPERATIONS ON BRAIN TUMOR.[1]

By William G. Spiller, M.D.,

Professor of Neuropathology in the University of Pennsylvania.

The discussion on brain tumor introduced by Bruns and Tooth[2] at the recent International Medical Congress, called forth some discouraging statements. Bruns said that about 30 out of 100 brain tumors are so situated that a radical operation may be advised; the localization is accurate and the tumor is accessible. He believed we may expect surgical success in 3 to 4 per cent. of all brain tumors. Tooth studied the records of 500 cases of brain tumor at the National Hospital, obtained during the years 1902 to 1911 inclusive. Of these about half came to operation. He thinks a high mortality is inevitable, but we must not be dismayed by it. We can reduce the mortality by judicious choice of cases for operation and by selection of the operation best suited for individual cases. The immediate dangers common to all growths, all situations, and apparently all operations, are shock, collapse, and respiratory and cardiac failure.

Many causes of disappointment will occur to anyone familiar with operations for brain tumor. The best known are incorrect diagnosis; infiltrating character, large size, and inaccessible situation of the tumor; mistakes in technique and impaired general vitality. Others equally important may be mentioned, but I desire in this communication to speak of the enlargement of the brain caused by tumor, the distortion of the brain especially from tumor in the posterior cranial fossa, and the acute swelling of the brain, probably an important element in the production of hernia cerebri, conditions which usually may be avoided by sufficiently early operation and proper technique.

[1] Read by invitation at a meeting of the New York Neurological Society with the Section on Neurology and Psychiatry of the Academy of Medicine, November 11, 1913. Lantern slides were used to illustrate the paper, but only a few are represented here.

[2] Proceedings of the XVII International Medical Congress.

It is important to remember that when tumor develops in the brain and exists for a long time alteration of the brain structure even in regions remote from the tumor may occur. Failure to take into consideration this alteration may lead to disappointment when operation does not produce the desired result. A tumor may be removed in whole or in part and yet symptoms may persist if a large part of the brain has undergone structural change. Late operation, and most radical operations for brain tumor are late from necessity, is likely at the best to afford recovery with defect, and this defect is dependent in a measure on the altered condition of the brain caused by tumor.

Increase of intracranial pressure is believed to be a cause of many of the general symptoms occurring with brain tumor, and it would seem from the writings of certain authors that the increase of pressure is attributed directly to the tumor and varies with the size of the tumor. There is a condition resulting from tumor to which little attention has been paid, and which is as important if not more so than the size of the tumor, viz., enlargement of the brain. This hyperplasia is not directly proportional to the size of the tumor, it may be of moderate degree, with a large tumor or sufficient to cause much enlargement of one cerebral hemisphere where the tumor is small. The hyperplasia may be the result of irritation either from pressure or possibly from some substance elaborated by the tumor, and is caused by overgrowth of neuroglia tissue. The condition is not unknown in medical literature, although little is said concerning it. Oppenheim remarks that the irritation which the tumor causes to the brain may lead to general swelling and increase in the size of the brain, upon which structural change, as proliferation of the neuroglia, follows. The disturbance of the normal relation of cranial capacity to weight of brain leads to functional alteration.

This hyperplasia of the brain may occur with almost any variety of tumor, and is not confined to glioma. It should not be confused with enlargement from glioma tissue, for it has not the appearance microscopically of tumor. It should not be confused with the acute brain swelling of Reichardt.[3]

Tumor external to the brain apparently does not lead to hyperplasia unless it causes much pressure upon the brain. In four cases of tumor of the cerebello-pontine angle I examined in which little pressure upon the brain was produced, no hyperplasia developed, but in another case in which a tumor of this angle caused considerable pressure upon the occipital lobe hyperplasia of the cerebral hemisphere of the same side was pronounced.

According to Reichardt, disease of the posterior parts of the

[3] Zeitschrift für die gesamte Neurologie und Psychiatrie, Referate und Ergebnisse, 1911, iii, 1.

brain in man may cause considerable swelling of the whole brain, and in this way choked disk may be produced. Sudden death may occur from tumor of the pons or medulla oblongata when choked disk has not been present, and this may occur from acute terminal brain swelling.

Reichardt believes the brain swelling as understood by him is not detectable with the microscope. The swelling may be confined to one cerebral hemisphere or to part of a hemisphere. It is probable that the swelling is caused by increased capacity of the brain tissue for fluid. The fluid enters into intimate combination with the brain tissue and is not recognizable as fluid, and the brain may even appear dry.

Increase in size of the brain may be from various causes: from increase of free fluid in the tissue spaces, from increase of histological elements, from hyperemia, etc., but this is not the brain-swelling of Reichardt. The true brain hypertrophy has no relation to the brain swelling, as the latter can appear and disappear rapidly.

The enlargement of a cerebral hemisphere, in which a tumor is situated, by irritation and proliferation of the neuroglia, does not seem to come under the designation of brain swelling as understood by Reichardt.

This hyperplasia of tissue near a tumor is not confined to the animal kingdom, but exists also in the vegetable kingdom. In the illustrations used in a lecture delivered before the Pathological Society of Philadelphia, by Edwin F. Smith, the tissue appeared to me to be proliferated about the tumor strands in plants much as the brain tissue becomes proliferated near a tumor.

The sudden fatal termination that occurs in some cases of tumor probably is a result of this enlargement of the brain, and of interference by the general increase of intracranial pressure with the important functions of the medulla oblongata. In other cases sudden death occurs from hemorrhage or injury of vital parts of the brain by the tumor, the pressing of the medulla oblongata against the edge of the foramen magnum, etc. In my experience, hemorrhage is not the most common cause of sudden death in brain tumor, although I have known it repeatedly to be diagnosed when sudden death occurred.

If the brain be examined by a neuroglia stain there will be found in some instances an overgrowth of neuroglia even in areas at a considerable distance from the tumor. Such increased density of tissue must interfere with the function of nerve fibers, and many of the remote symptoms of tumor probably are from this cause as well as from disturbance of function in associated tracts (diaschisis). The picture given by Rosental[4] in his article on pseudotumor,

[4] Zeitschrift für die gesamte Neurologie und Psychiatrie, 1911, vii, No. 2, 170.

representing neuroglia proliferation, is much like certain sections from one of my specimens (Fig. 1), but I have not been able to demonstrate proliferation of the neuroglia in all cases. A neuroglia proliferation of moderate intensity is not easily shown even with a neuroglia stain. While I believe that in many cases the permanent enlargement of the brain in association with brain tumor is the result of proliferation of the neuroglia, in whatever way it may be produced, I wish to emphasize the fact that this enlargement of one cerebral hemisphere even if produced in some other way than by proliferation of neuroglia is likely to cause symptoms in addition to those caused by the tumor.

Some of the remote symptoms may be produced by changes in the nerve cells from the tumor. Redlich[5] found in some cases of

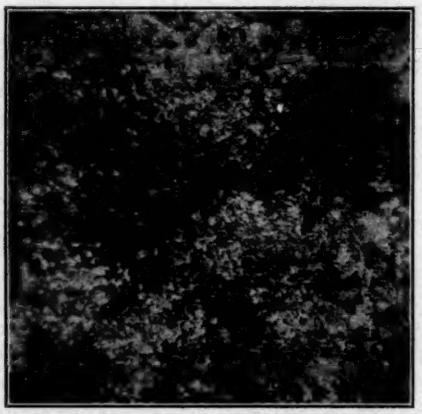

FIG. 1.—Photograph of a section from the centrum semiovale below a small tumor of the parietal lobe. The whole cerebral hemisphere of this side was much enlarged. The neuroglia is shown proliferated in irregular masses. (Mallory's neuroglia stain.)

brain tumor with mental symptoms alteration of the nerve cells and nerve fibers in pieces taken from different parts of the brain, but he could not find the changes in the glia spoken of by Reichardt, and no increase in neuroglia fibers except near the tumor. The changes Redlich found resembled those of senility, and did not satisfactorily explain the mental symptoms associated occasionally with brain tumor.

It may be that hyperplasia of the brain is an important cause of impairment of mentality in some cases of brain tumor. I have

[5] Obersteiner's Arbeiten, vol. xv, part 1.

known large endotheliomas to exist without any impairment of intellectual power, and in such cases one finds that the tumor has grown slowly, has caused much atrophy of the underlying brain, but may not have led to hyperplasia of a large part of the brain. Some of my cases of enlargement of a cerebral hemisphere presented symptoms which it would be difficult to attribute to the tumor directly. In one, a glioma (449) (Fig. 2) of the pons caused considerable

FIG. 2.—Enlargement of one cerebral hemisphere caused by a glioma of the pons.

enlargement of one cerebral hemisphere. The patient presented some symptoms which it would be difficult to explain entirely from a pontine lesion. She was hungry all the time and childish. Excessive hunger as a sign of brain lesion I have observed several times.

In another (422) (Fig. 3), a glioma was found in the region posterior to the right optic thalamus. The portion of the right hemisphere in front of the tumor was considerably enlarged. The speech was slurring, and tests words were pronounced with difficulty. The

memory was poor and the man was easily confused. He acted queerly, attempted to disrobe in public, and did not know how to put on his clothing. He had been alcoholic, so that the effects of alcohol cannot be eliminated, yet I believe that some of his symptoms may have been caused by the hyperplasia.

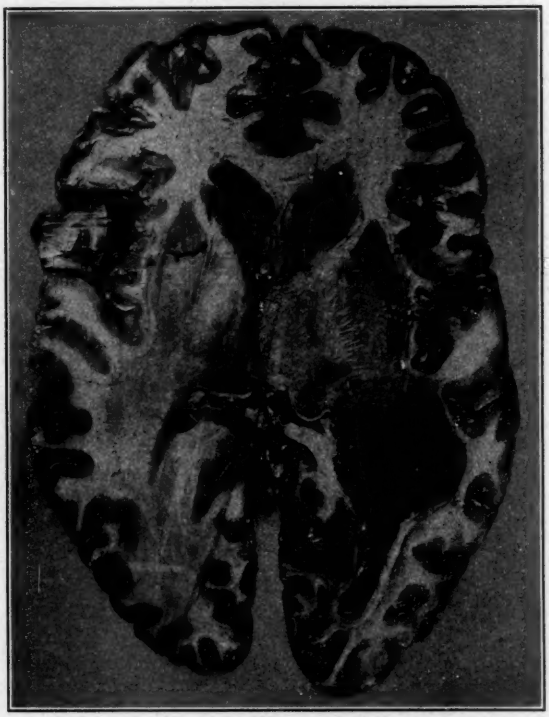

FIG. 3.—Glioma in the region posterior to the right optic thalamus. The same side in front of the tumor is much enlarged.

Another case was interesting in that death occurred very suddenly; the tumor was small, but the whole cerebral hemisphere of the same side was much enlarged. In still another (Keesler), sudden death occurred and a small tumor was found in the left lateral lobe of the cerebellum, and another, also small was found in the right motor region of the cerebrum, but no hemorrhage was revealed.

It is important to state that the enlargement in all these cases was not from distortion as a result of pressure from a tumor. The

parts preserved their relative positions, but were considerably enlarged.

Indeed one of the greatest enlargements of the brain I have observed was from a small tumor of the parietal lobe measuring in a transverse section of the brain 2 x 3 cm. The enlargement of the cerebral hemisphere on the side of the tumor was as great as that represented in Fig. 2. Fig. 1 represents a section from this case.

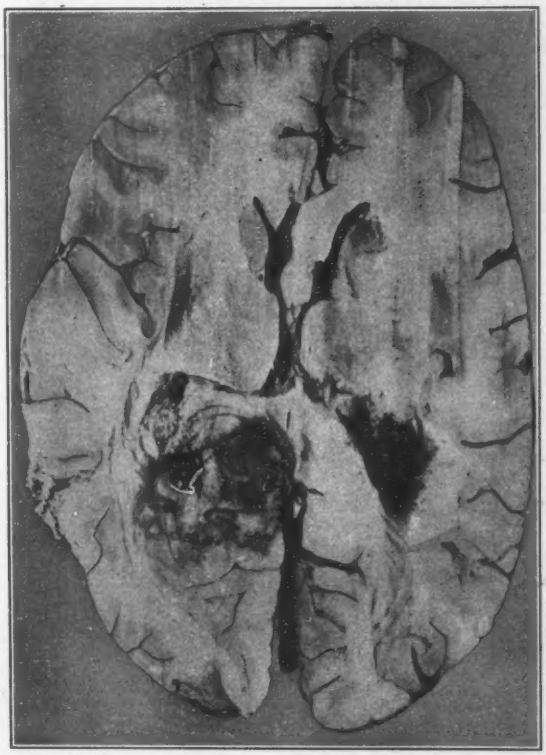

FIG. 4.—Tumor of the occipital lobe. The cerebral hemisphere containing the tumor is much enlarged.

Distortion of certain parts of the brain is a grave complication of tumor. I have already discussed this in a recent paper in *Brain*. The displacement of the cerebellum and occipital lobes complicates operation, as sudden relief of pressure probably has injurious effects on parts distorted gradually. The medulla oblongata may

be so distorted that with the upper cervical cord it forms a half circle. This occurred in a brain from a patient in my service at the Philadelphia General Hospital (Fig. 5). Cranial nerves in the region of the medulla oblongata are liable to be stretched gradually by such distortion, and the effect of this stretching on the pneumogastric may be serious. The distortion in this case was explained by the pressure from a large cyst occupying the greater part of

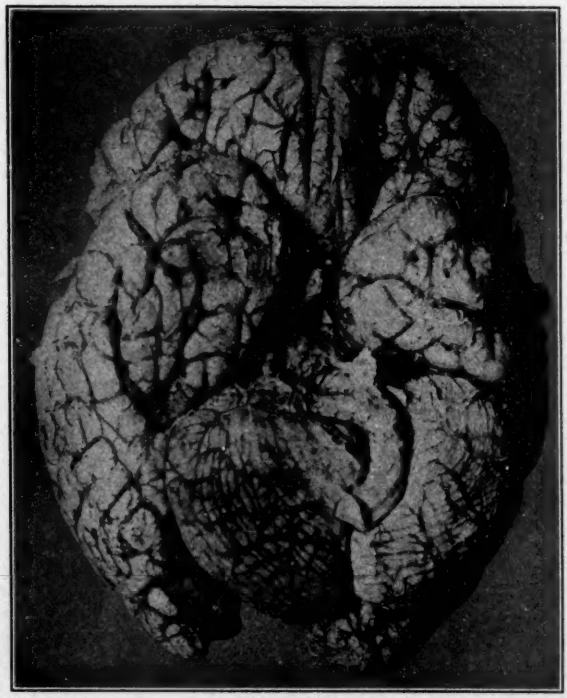

FIG. 5.—Atrophy of the left lobe of the cerebellum and distortion of the medulla oblongata, caused by a large cyst of the left cerebral hemisphere. Displacement of the medulla oblongata of this degree is likely to affect the cranial nerves connected with it.

the left cerebral hemisphere, communicating with the lateral ventricle of the same side, and causing atrophy by pressure of the left cerebellar hemisphere. The cyst evidently was from occlusion of the anterior cerebral artery, as its extent corresponded to the distribution of this artery as given by Beevor. One might well consider whether it would not be desirable to delay the removal of a large tumor causing much displacement of the brain, after it had been revealed at operation, until a later operation had

given time for the brain to readjust itself in some degree to the changes of pressure following the opening of the dura.

Hernia cerebri is a serious complication of operation for brain tumor. Where it results from decompression it has been supposed to be indicative of the degree of intracranial pressure and to show to what extent intracranial pressure has been relieved. This view is not entirely correct. Intense intracranial pressure possibly may be more liable to cause hernia than intracranial pressure that is more nearly normal, and yet much hernia may develop where there has been no decided increase of intracranial pressure. A large hernia occurred in one of my cases in which a thrombus of the inferior petrosal sinus of long duration had caused atrophy of the adjoining pons, the intracranial pressure could not have been greatly increased, nevertheless a large hernia developed. It seems probable that in such cases acute swelling of the brain in the sense of Reichardt may be responsible for the hernia.

A hernia may cause pressure against the edges of the opening in the skull, with occlusion of vessels and softening of the parts of the brain implicated in the hernia, causing in this way hemiplegia and other grave symptoms.

I am indebted to Dr. A. J. Smith for the photographs.

THE MECHANISM OF THE CIRCULATORY FAILURE IN DIPHTHERIA.

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In the course of acute infections it is well known that the patient may die with symptoms somewhat like those of surgical shock. The blood-pressure falls, the pulse becomes weak and small, the skin is pale or cyanotic about the nose and ears, sweating and vomiting ensue, and with shallow respiration and general collapse, the heart stops beating.

The discussion as to the mechanism of this disturbance is so well known that only the briefest *résumé* need be given here. It had long been thought from clinical observations that the affection might be one of the vasomotor apparatus rather than the heart itself, and Romberg, Pässler, Brühns, and Müller attempted to prove this in the case of diphtheria, pneumococcus, and pyocyaneus infections by experimental studies. In these studies they relied upon certain methods which aimed to demonstrate that the heart would regain its activity if the failure of the vasomotor apparatus

were overcome in some way, and that those things which ordinarily caused vasomotor reactions were ineffectual. Thus they found that the mechanical expression of the blood from the splanchnic veins into the heart would restore for a time the aortic pressure, and with that the coronary blood-supply, and thus the nutrition and activity of the heart. The same could be produced by compressing the aorta. Barium chloride still caused the vessels to contract, but sensory stimuli had lost their effect. They, therefore, concluded that the circulatory failure was not due primarily to injury of the heart, but rather to the paralysis of vasomotor centres in the brain, which, causing a lowering of arterial resistance, quickly affected the heart through the diminished coronary supply to the heart wall. Romberg especially pointed out the fact that if the heart were at fault all these tests should fail.

Then Stejskal criticized their methods, showing that abdominal massage could increase arterial pressure even in a dead animal, and that its effects are very transient. He believed that the heart itself is directly injured, and fails on that account. Gottlieb supported this view to some extent, believing that the withdrawal of blood from the coronary circulation need not kill the heart so rapidly, since a heart may be kept for hours after the animal's death and then revived by perfusion. He therefore concluded that death probably was due to respiratory stoppage, with subsequent failure of the heart, due to its injury by the poison.

Rolly and Pässler later reviewed the subject, and seem to admit the force of Stejskal's objections as to the abdominal massage; and though they maintain the idea that the injury to the heart is through malnutrition, they state that it becomes very susceptible to other injuries. Other writers, whose papers are referred to below, lean to one or the other view or accept the idea that both vasomotor paralysis with its consequences and direct injury to the heart wall occur.

In the course of a study of the mechanical conditions present in aortic insufficiency, a plan was devised by which the influence of the vasomotors might be almost entirely eliminated and the work of the heart studied by itself.[1] This plan consisted in simply dividing the aorta near its root and connecting it with a long rubber tube, ending in a curved glass outlet, which could be elevated to any height upon a graduated upright pillar. The aortic pressure could in this way be set at any point according to the height to which the heart must drive the blood against the force of gravity. The blood which escaped fell into a cistern and returned through another long tube to the distal part of the aorta. Of course, by applying this arrangement to an animal in the collapsed condition which follows poisoning with the diphtheria toxin, the injurious effects of paralysis

[1] W. G. MacCallum, Johns Hopkins Hosp., Bull., 1911, xxii, 107.

of the vasomotors would be removed at once, and if the theory of the Leipzig school be correct, the heart should return to its normal activity and the animal continue to live.

The following protocols will illustrate the results of this experiment:

Dog 1.—Weight, 8.9 kg. April 25, 1911, 1 A.M. The dog was given 1 c.c. diphtheria toxin intravenously. At 11 A.M. the animal was found lying sick in the cage. Carotid pressure was taken at 11.30. Chest was opened and the circulation arranged as described, the outlet being set at 130 cm., which was the carotid pressure before the operation. The heart beat well for two hours, after which there appeared great edema of the lungs, and the heart dilated and stopped. All of the organs were found to be edematous, and showed numerous ecchymoses. The heart beat regularly throughout, and the output was well maintained.

Dog 6.—Weight, 6.6 kg. May 3, 1911, 12.45 A.M. The dog was given 0.75 c.c. diphtheria toxin intravenously. At 1 P.M. the carotid pressure was taken, the aorta cut, and external circulation arranged. This was finished at 1.20 P.M., and the heart beat well until 3.10 P.M., when there was extreme edema of the lungs and of other organs. In the heart, which was otherwise grossly normal, there were many hemorrhages. Here as in the first case the heart continued active for two hours.

Dog 7.—Weight, 10.3 kg. May 5, 1911, 12.30 A.M. The dog was given 2 c.c. diphtheria toxin intravenously. At 12 noon the dog was apathetic and drowsy. At 2 P.M. it vomited and appeared very weak. Artificial or external circulation arranged at 2.40 P.M. and the heart beat at a pressure of 110 cm. blood until 5.35 P.M. At times the heart began to collapse and beat with great excursions, driving out relatively little blood. One dose of digitalin and strychnine was given, which restored it to its normal beat. During the latter part of the three hours there were violent general convulsions.

Dog 13.—Weight, 6 kg. April 2, 1913. The dog was given 3 c.c. diphtheria toxin intravenously at 10.30 A.M. It was found very sick at 4 P.M., and at 4.45 P.M. the external circulation was arranged, after which the heart beat quite well until 7.20, when the supply of blood failed and the experiment was stopped. There was some irregularity in the action of the heart, but on the whole it beat strongly for two hours and thirty-five minutes.

In order to have a good control observation, two dogs of the same size were given the same dose at the same time. It was intended to show that with the aid of the maintenance of arterial pressure one could be kept alive long after the other had died.

Dog 14 A, weight 10,560, female, and Dog 14 B, weight 10,900, male. Each dog was given 4 c.c. diphtheria toxin intravenously at 8 A.M., April 3, 1913. Both dogs had vomited and were depressed

and weak at 5 P.M. Dog A was found lying stretched out stiffly and not breathing. Heart not beating. Artificial respiration was begun. Carotid pressure was very low. It was attempted to establish the external circulation, but through an accident the dog died. By this time, 5.35 P.M., Dog B was almost dead, and lay inert. Reflexes were gone, the eyes rolled about, and there were convulsive twitchings. External circulation was established at 5.45 P.M. and tracings of the heart-beat were taken until 8.35 P.M., a period of two hours and thirty-five minutes when the heart stopped, apparently only because it finally became necessary to use blood which had been kept several days.

Dogs 15 A and B, weighing respectively 11 and 10.3 kg., were given 4 c.c. diphtheria toxin at 8 A.M., April 8, 1913. At 3.55 P.M. both dogs were almost dead, lying quite apathetic with complete loss of reflexes and occasional convulsions. Dog A, whose blood pressure as taken from the carotid was very low, about 60 cm. of blood, was arranged with the external circulation and the outflow tube set at 85 cm. The heart-beat improved at once and continued from 3.30 to 4.40 P.M. In the meanwhile Dog B died at 3.20 P.M. The character of the pulse of Dog A, as seen in the tracing, varied spontaneously being rapid and strong at times and producing an abundant outflow, while at other times there was a slower collapsing beat, which propelled relatively little blood to the outflow. After one hour and ten minutes it became distended during a convulsion, and could not be made to beat again. It seemed that in this case at least the heart itself had been injured by the poison.

For comparison normal dogs were subjected to the same operation as shown in the following protocols:

Dog 2.—Weight, 6.9 kg. Anesthetized with chloretone April 28, 1911. External circulation complete at 3.30 P.M.; pressure set at 130 cm. blood, which equals about 100 mm. mercury. At 4.45 P.M. there was much oozing from cut tissues, and the heart became distended. Pressure lowered to 53 cm. and heart beat again. Some edema of lungs and of other tissues. Given a dose of digitalin, after which heart beat well until 6.30 P.M., when the dog was killed.

Dog 5.—Weight, 9.9 kg. Anesthetized with ether May 2, 1911. The external circulation was arranged through one intercostal space at 3.20 P.M., and the outflow tube was set at 130 cm. of blood. The heart beat well until 6.20, when the dog was killed.

The actual output per minute of each of these hearts cannot be accurately determined from the curves produced by this method, because much of the blood circulates through the head and forelimbs, but since the records were all made in the same way, it will give some idea of the character of the heart's work after diphtheria poisoning to compare the output from the artificial aorta with that in the case of the normal dogs.

Dog 7 (Diphtheria).—Weight, 10.3 kg. Outlet was set at 110 cm.

Operation at	2.40 P.M.				
	3.30 "	100 c.c.	were delivered in	26	seconds.
	4.00 "	100 c.c.	"	28	"
	4.30 "	100 c.c.	"	32	"
	4.35 "	100 c.c.	"	30	"

Dog 1 (Diphtheria).—Weight, 8.9 kg. Outlet was set at 130 cm.

Operation at	11.30 P.M.				
	12.00 M.	100 c.c.	were delivered in	18	seconds.
	12.30 A.M.	100 c.c.	"	19	"
	1.00 "	100 c.c.	"	19	"
	1.30 "	100 c.c.	"	18	"

Dog 2 (Normal).—Weight, 6.9 kg. Outlet was set at 130 cm.

Operation at	3.30 P.M.				
	3.50 "	100 c.c.	were delivered in	21	seconds.
	4.30 "	100 c.c.	"	20½	"
	5.45 "	100 c.c.	"	34	"

Dog 5 (Normal).—Weight, 9.9 kg. Outlet at 130 cm.

Operation at	3.00 P.M.				
	3.45 "	100 c.c.	were delivered in	35	seconds.
	4.30 "	100 c.c.	"	29	"
	5.00 "	100 c.c.	"	30	"
	5.30 "	100 c.c.	"	29	"

From these it will be seen that the actual work of the diptheria hearts was at least as good as that of the normal hearts.

It is probable that if the conditions were absolutely perfect and the exposure, use of defibrinated blood, etc., avoidable, it would be possible to keep a normal heart driving the external circulation for a longer time than three hours. It is probable, too, that even under the present circumstances a normal heart treated in the way the hearts of the poisoned animals were treated would beat a little longer and a little more steadily than they. But the difference is so slight that, while it seems probable from such spontaneous irregularities as occurred in the case of Dog 15 A, that the heart itself was injured by a large dose of toxin, it was clear enough that it was still able to carry on the circulation for two or three hours against a high pressure, a thing which is vastly different from mere beating in a profusion apparatus.

It might be objected that the use of fresh blood would restore the heart by washing away the toxin, but in all these experiments the blood of the animal itself was returned to the circulation and was merely diluted. At any rate, Decroly and Ronnse showed that diphtheria toxin injected into the blood stream disappears completely after four to seven minutes, so that the injury is probably determined in some early part of the latent period. Rolly in his

experiments found that washing out an isolated heart with fresh blood had no effect in postponing the death of the heart, and apparently this was true. But while Rolly was unable to revive a poisoned heart, it proved to be not impossible, as the following protocols show.

Dog 16.—May 13, 1911. Isolated heart from normal dog perfused with Ringer's solution beat for two and a half hours at a rate of about 103. The drops of diphtheria toxin injected into the circulating fluid caused an immediate increase in rate to 200 after which the heart continued to beat for two hours longer at a rate of about 150.

Dog 17.—May 24, 1911. Isolated heart from normal dog perfused and was beating for one hour at a rate of 98. At 12.25 P.M. 1 c.c. of diphtheria toxin was added to perfusion fluid. This was followed by a marked stimulation of force and rate which rose to 112. The heart continued to beat until 3.30 P.M., when after a period of dissociation of auricular and ventricular beats it stopped.

Dog 18.—May 25, 1911. Weight, 5.7 kg. The dog was given 1 c.c. toxin intravenously at 11.10 A.M. At 6 P.M. the carotid pressure was low. At 10.30 A.M. the dog was extremely ill, and died at 10.55 A.M. The heart was found to have stopped beating. It was removed from the body and perfused with Ringer's solution, upon which it began to beat at 11.10 A.M., and continued to beat well for one hour and ten minutes.

Dog 19.—May 25, 1911. Weight, 5.9 kg. The dog was given 1 c.c. diphtheria toxin at 11.30 A.M. At 5.45 P.M. it was killed with ether and the heart excised and perfused with Ringer's solution. From 6.45 to 10.55 P.M. the heart beat strongly and regularly at a rate of about 90 to 110.

Dog 20.—May 25, 1911. Weight, 6.8 kg. Given 1 c.c. diphtheria toxin at 11.45 P.M. At 1 P.M. the next day the dog was nearly dead. It was killed at 1.35 P.M. and the heart perfused. The rate was somewhat irregular, varying from 44 up to 110, but for the greater part of the next two hours it beat strongly at about 62, stopping at 4.50 P.M.

Dog 21.—May 28, 1911. Weight, 7.8 kg. Given 2 c.c. of diphtheria toxin intravenously at 9.45 P.M. At 11 A.M. the next morning the dog was found dead, although alive and apparently fairly well a few minutes before. The heart was excised, but could not be started in perfusion apparatus until 11.50. At first there was fibrillation, but this was stopped by injection of potassium chloride, after which it beat somewhat irregularly until 2.15 P.M., a period of two hours and twenty-five minutes.

Dog 22.—May 30, 1911. Weight, 8.7 kg. Given 2 c.c. diphtheria toxin at 11 P.M. The next day at noon the dog died; the splanchnic vessels were much dilated. The heart was perfused at 12.15 P.M. and beat fairly well for three hours and forty

minutes, becoming edematous at last. For most of the time the rate was 96 to 100, but several times a spontaneous heart-block occurred, with a 1 to 2 rhythm, which each time suddenly changed back to the 1 to 1 rhythm.

Dog 23.—May 30, 1911. Weight, 8.2 kg. Given 1.5 c.c. diphtheria toxin at 11 P.M. The next day at 3.15 P.M. the dog was evidently dying. It was killed with ether and the heart excised and perfused. Perfusion began at 4 P.M., and the heart beat with varying rate until 7.20, a period of three hours and twenty minutes.

Dog 24.—June 1, 1911. Weight, 7 kg. Given 2 c.c. diphtheria toxin at midnight. At 11 A.M. the next day the dog was *in extremis*. The carotid pressure was very low. Etherized, and the heart was excised and perfused. It beat slowly from 11.20 to 2.25 P.M., about three hours, at a rate of about 52.

Dog 25.—June 2, 1911. Weight, 7.2 kg. Given 2 c.c. diphtheria toxin at midnight. At 1.15 P.M. the next day dog was very sick. Alcohol by stomach-tube had no effect upon the blood pressure, which sank until the dog's death at 2 P.M. At 2.10 P.M. the heart was perfused and beat normally at a rate of about 94 for three hours and thirty minutes, stopping at 5.40 P.M.

Dog 26.—June 3, 1911. Weight, 8.9 kg. Given 2 c.c. diphtheria toxin at 11.15 P.M. The next morning, at 9.30 the dog was found dead but not cold. Rigor was beginning. At 9.45 A.M. the excised heart was perfused and beat until 10.40 A.M. at the rate of about 100, rather feebly and irregularly.

In all these hearts the beat was rather feeble as compared with that of the perfused normal heart, and fibrillation seemed likely to occur. The note reads: "There is no comparison between the perfused normal heart and the diphtheria hearts, all of which are feeble and apt to go into fibrillation." Nevertheless, although one may receive the impression that the hearts from the poisoned animals are rather weak and apt to be irregular, it is clear that they continue to beat for several hours after they have shown every sign of failure in the body of the dying animal, if only the pressure of nutritive fluid be maintained in the coronary arteries. Indeed, the animal may be allowed to die, and an hour after its death the heart can be revived and will beat for a long time. All of this seems to show fairly well that the death which occurs in the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although that may play some part in the process.

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BLEEDING IN TYPHOID FEVER.

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It is generally recognized that the occurrence of hemorrhage in the course of typhoid fever is a serious matter, especially when it appears late in the disease. The degree of seriousness of this complication, however, has been differently estimated by writers, and one finds Trousseau and Graves constantly quoted as declaring that it was not an unfavorable event and sometimes even of advantage, while Murchison, Dieulafoy,[1] and others state that it is a bad omen and not even of transient benefit. Thus, on the one hand, Leibermeister[2] writes: "If at the end of the third or fourth week a large intestinal hemorrhage appears, it may occur that the marked fall of temperature with it will have a favorable influence upon the enteric phenomena present, recovery steadily advancing from that time on. These are the cases that have led competent observers (Graves, Trousseau) to maintain that intestinal hemorrhages are by no means unfavorable in enteric fever, but are rather of favorable prognostic import." On the other hand, Murchison wrote: "Although I have seen patients recover after a profuse hemorrhage, I have never seen the slightest benefit from it."[3]

It is admitted by every writer that the temperature often tends to fall after a hemorrhage, but most state that along with this lessening in the temperature there is a rise in the rate of the pulse. Thus, for example, Curschmann[4] says: "In those cases in which the patient does not die during the first copious hemorrhage the clinical picture becomes alarmingly altered. The skin acquires a waxy

[1] Text-book of Medicine (translation), ii, 1626.
[2] Modern Clinical Methods in Infectious Diseases, p. 30; The Physiology of Blood-letting, British Med. Jour., 1910, i, 104.
[3] Sir Thomas Watson, Principles and Practice of Medicine, ii, 881.
[4] Typhoid and Typhus Fevers, Nothnagel's Encyclopedia of Practical Medicine, p. 223.

pallor, there is relaxation of the features, the pulse becomes small and shows greatly increased frequency, lividity and coldness of the extremities and possibly syncope appear. With the rapid increase in the pulse frequency there is generally associated a rapid reduction in the bodily temperature. The curve may be observed to decline from 40° or 41° C. to far below the normal—to 35° C. and below—in a few hours. This characteristic intersection of the pulse and temperature curves is of grave prognosis." He adds later, "Quite rarely I have seen the pulse-frequency fall parallel with the temperature curve—a condition that is without doubt to be considered as a favorable prognostic sign." Again, T. McCrae,[5] in speaking of hemorrhage in typhoid fever, says: "The temperature usually falls, and the drop may be as much as 10° and to below normal. Still, even a sharp hemorrhage may have no effect on the temperature. The pulse-rate rises, and with it the quality alters. At first somewhat bounding, later it becomes small and somewhat running." He also says later: "That results of hemorrhage are very various, and there is no doubt that some patients do seem to be benefited. These are usually robust and but slightly toxic. The temperature curve may be lower, the pulse not increased in rate or even decreased, and the whole character of the attack milder." One can easily realize that if the hemorrhage be very profuse a state of shock will ensue, with a marked fall in the temperature and rise in the rate of the pulse, along with all the other signs of an acute and profound anemia; but the rule seems to be, certainly in our series, that the temperature and pulse-rate fall together, with, as will be shown, a frequent improvement in the general condition of the sufferer.

It is difficult to believe that two such keen observers as Trousseau and Graves could have meant that bleeding in typhoid fever was not a serious thing, and probably Flagge was right when he wrote,[6] "Probably the real basis of their opinion was the fact that a good many patients recover from it, or, in other words, that it was not so often directly fatal as might have been anticipated." Certainly any statistical study of the disease makes it evident that the cases which have had hemorrhages have a much higher death rate than have others not so complicated. Thus in studying the last 1591 cases of typhoid fever treated in the Toronto General Hospital it appears that the mortality was 8.67 per cent. over all, but that the death-rate among those reported as having had one or more hemorrhages was 37 per cent. This latter figure is almost the same as occurred in Cruschmann's series at Leipsic, which was 38 per cent.,[7] while in Strümpell's forty-five cases of hemorrhage in typhoid fever it was 42.2 per cent. In our series, if we exclude the cases

[5] Osler's Modern Medicine, i, 127.
[6] J. Hilton Fagge, Principles and Practice of Medicine, i, 179 and 180.
[7] Osler's Modern Medicine, p. 127.

that had bleeding, we find that the mortality of the remaining 1464 cases was only 6.3 per cent.

The question here arises as to why enteric fever complicated with hemorrhage should have such a higher death-rate. The ill-effects of bleeding may be due (1) to the actual loss of blood, which may be directly fatal (as it was in eight out of Strümpell's nineteen deaths in typhoid complicated with hemorrhage), or the anemia may so weaken the patient as to lay him open to other complication, or (2) the bleeding may denote perforation, and in any case is usually significant of a severe infection. If it were not for these two classes of dangers, which are more or less imminent in hemorrhage cases, the loss of blood, if of moderate amount, might be welcome. Many writers, for example Leibermeister and McCrae, not to mention Trousseau and Graves, have remarked how often patients seem to improve after moderate hemorrhages, and if it were not for the dangers looming up of the bleeding becoming uncontrollable or being a precursor of perforation, probably most physicians would be pleased rather than otherwise with the at least temporary benefit which so often accrues.

The appended twelve charts are taken from among the cases of intestinal hemorrhage (with one exception where the bleeding was through venesection) that occurred in our series at the Toronto General Hospital, and they show how the bleeding was followed by a more or less marked fall not only in the temperature but also in the pulse rate. They are perhaps the best examples, but most of the other one hundred and fifteen charts of cases with bleeding showed more or less of the same thing. They do not, of course, show the improvement in the general condition that was so often noted, but a perusal of the epitomes of the histories will make this evident. The notes of progress are exactly as they were made at the time by members of the staff and the house physicians. It will be noted that the improvement in the temperature and pulse curves, while often transient, in some cases may last for days and may even usher in convalescence. It is impossible in the face of such evidence to agree with Fagge when he says: "According to Liebermeister, hemorrhage also diminishes the pulse, and is often attended by a marked amelioration of the cerebral symptoms. But all these effects are transitory, for by the end of twenty-four hours the fever is as high or higher than before the hemorrhage." Or with Murchison, who wrote: "I have seen patients recover from profuse hemorrhages. I have never seen the slightest benefit from it."

It is difficult to explain how the good effects that may follow a hemorrhage come about. There is no doubt, however, but that it produces a profound effect upon the whole bodily economy. Thus bleeding has been shown to bring about an increase in the flow to urine;[8] to greatly increase the intake of oxygen, with pro-

[8] Potochi, Revue Pratique d'Obstetrique et de Gynécologie, January 20, 1911, No. 1, p. 28.

portionate raising of tissue-oxidation.[9] It hastens the coagulation time of the blood more than does any other single agent with which we are acquainted.[10] Roux and Vaillard showed in 1893 that it produced a rapid increase in the antibodies contained in the blood, and Dreyer and Schroeder, of Copenhagen, about four years ago, demonstrated that it increases the specific antibodies in typhoid and paratyphoid, both in experimental animals and in man. H. Whitehead[11] fully confirmed this two years ago in a study of typhoid complicated by hemorrhage, in which the agglutinating power of the blood was enormously raised by the bleeding. Further, in toxic conditions, such as uremia and other less-defined states, states, where there is high blood pressure, bleeding appears to in some way lessen the toxemia, and possibly in typhoid it may have some similar effect.

Finally, Whitehead, in his paper two years ago, suggested that the good effects of hemorrhage in typhoid fever might be attained and the evil ones (associated with intestinal hemorrhage) avoided by the timely use of venesection in those cases which are not doing well on account of severe infection and toxemia, and with this suggestion I heartily concur. Of course, in the days when venesection was considered to be a panacea for almost all ailments, cases of typhoid fever must have been bled, but it is impossible to get at any reliable data as to the results, as at that date typhoid fever was not differentiated from other cases of continued fever. Even Marshall Hall, who is considered to be the great opponent of bleeding, and who is given the credit of having brought about the almost complete abandoment of this time-honored method of treatment, states that in severe and eruptive fevers[12] from six to fourteen ounces of blood should be removed, so that it is not likely that cases of typhoid fever escaped.

So far only one case can be shown in our series (Case VII), but the sequence of the venesection was there most marked. Theoretically the method appears to be indicated in severe cases and if the removal of blood by venesection be a moderate one, say of six to fourteen ounces, as was recommended by Marshall Hall, it can do no harm and may possibly be productive of great good.

EPITOME OF CASES.

CASE 1 (Not yet filed).—Female, aged twenty-two years. Admitted October 1, 1911. Duration of illness, about two weeks. Was dull and drowsy; flushed.

[9] Beaumont Small, Reference Handbook of the Medical Sciences, ii, 71.

[10] Rudolf and Cole, The Coagulation Time of the Blood in Various Diseases, AMER. JOUR. MED. SCI., October, 1911.

[11] Intestinal Hemorrhage in Typhoid Fever, Lancet, 1911, ii, 1067.

[12] Marshall Hall, The Cyclopedia of Practical Medicine, 1833, quoted by D'Arcy Power, Practitioner, 1909.

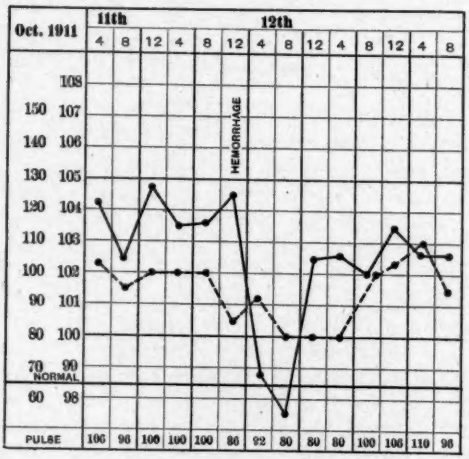
October 7. Vomited a great deal, and was dull and very toxic.

October 12. Very dull and toxic. Vomited twice. At 5.30 A.M. there was a profuse hemorrhage from bowel.

October 13. Brighter. Pulse, 92. Temperature, 98.6. Systolic blood pressure, 72; diastolic, 45.

October 19. Brighter. Toxemia not so marked. Temperature, 102.4°; pulse, 92; respiration, 22.

October 31. Quiet; sleeping well. No vomiting since October 12. Steadily improved, and was discharged well on January 21, 1912.



CASE I

CASE II (Vol. xxxix, Case 6088).—Male, aged thirty-five years. Admitted October 4, 1909. Duration of illness, about two weeks. Was in fairly good condition. Abdomen not distended; pulse very dicrotic.

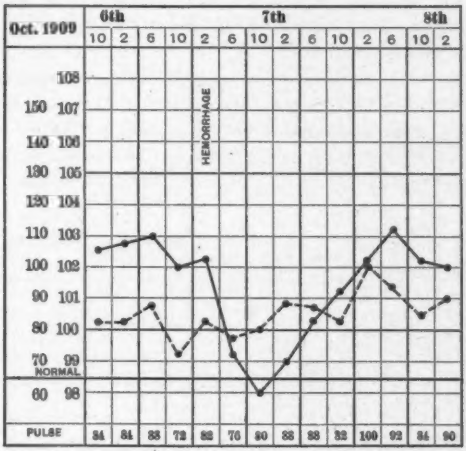
October 6. Chilly and free sweats. Lips dry. Tongue clean and red. Later in the day was drowsy and had severe headache and abdominal distress.

October 7. In early morning and again just before noon the patient complained of chilly feelings, and sweated. Was quite restless, and had severe abdominal pain, with no rigidity or tenderness. Some nausea. Bowel movement at noon showed small amount of dark blood. Half an hour later a large amount of blood. Pulse not changed. An hour later a third hemorrhage—very large. No change in pulse until then, when it became rapid, and he had a general faint feeling, blanched and hands clammy, and half an hour later had a profuse perspiration. At midnight the pulse-rate was not changed; temperature, 99°.

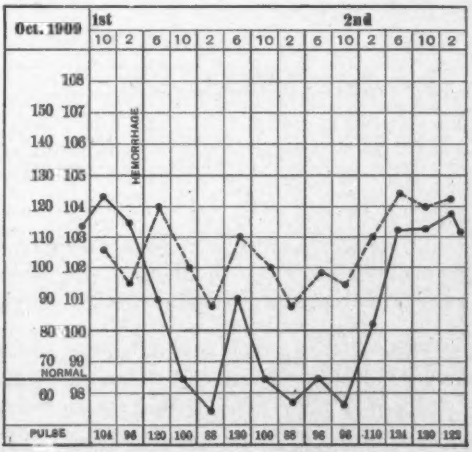
October 8. Slight hemorrhage at 9 A.M. This recurred slightly for two days. Pulse-rate not altered for the worse.

October 11. General condition satisfactory. Temperature running at a satisfactory height.

November 13. Uninterrupted progress. Soon after he left the hospital well.



Case II



Case III

CASE III (Vol. xlvii, Case 6917).—Female, aged twenty-eight years. Admitted September 19, 1909. Duration of illness, about one month. Fairly severe attack.

September 26. Very drowsy and slept most of the day. Tongue drying. Some diarrhea (5). Abdomen distended.

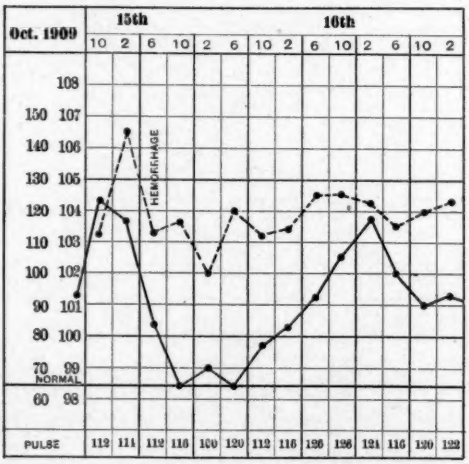
September 29. Abdomen distention marked. Pulse dicrotic. Patient very dull.

October 1. Hemorrhage occurred in night and today several times. Pallid. Skin cold and clammy. Pulse of poor quality. Respiration sighing.

October 2. No more hemorrhage. Patient brighter.

October 4. Abdomen distended. Respiration sighing. Pallor marked but pulse unchanged. Resting well at night.

October 5. Slight hemorrhage today. This patient eventually left the hospital well.



CASE IV.

CASE IV (Vol. xlvii, Case 6926).—Male, aged thirty years. Admitted September 30, 1909. Duration, five days. Severe case, with high fever, easily lowered always by three grains of aspirin.

October 14. Has a restless night; tried to get out of bed, and talked to himself. Subsultus marked. Sweated freely. Very drowsy, but rational until tonight; sitting up in bed and trying to get out of it. 8 P.M.: pulse 120; respiration, 20; temperature, 105°, 10 P.M.: pulse, 104; respiration, 20; temperature, 100.2°. Pulse and abdomen good.

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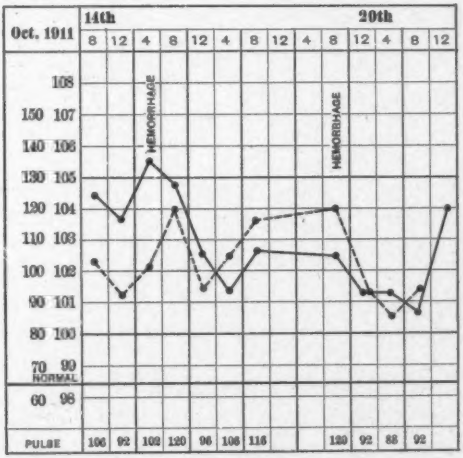
October 15. Profuse hemorrhage at 6 A.M., which was bright red. Pulse irregular and intermittent, small and thready. Profuse sweating. 8 A.M.: pulse, 144; respiration, 32; temperature, 103.2°. At noon patient was quite bright; pulse, 112; respiration, 24; temperature., 100.2°. 4 P.M.: pulse 116; respiration, 28; temperature, 98.2°. 8 P.M.: pulse, 120; respiration, 20; temperature, 99°. Pulse of better quality. Another hemorrhage in evening. Midnight: pulse, 120; respiration, 20; temperature, 98.3°.

October 16. Noon: pulse, 120; respiration, 24; temperature, 101.1°. Patient brighter. Pulse of better quality than in morning. Patient very quiet; slept most of the day. Abdomen and pulse satisfactory. After this the patient had a number of hemorrhages at intervals of several days. Each one was followed by a temporary drop in temperature and pulse-rate and an improvement in general condition. He eventually completely recovered.



CASE V

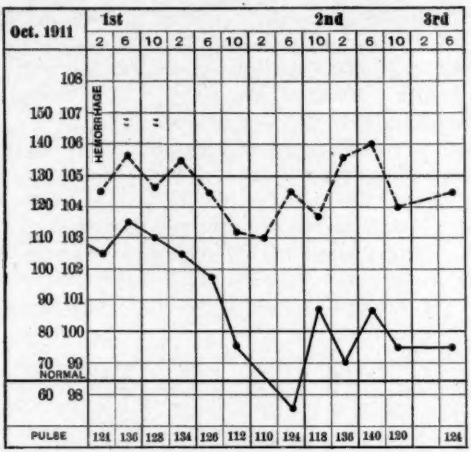
CASE V (Vol. lxxiv, Case 9772).—Male, aged twenty-six years. Admitted October 9, 1911. Duration of illness, ten days. Dull and heavy, and covered with rose spots. Lips dry. Temperature, 104.8°.

October 14. Very dull and heavy. Perspiring freely. Respiration, 36; pulse, 105. Had a free hemorrhage this morning.

October 15. Patient appears to be improved; less toxic. Tongue very dry.

October 16. Pale and hard to arouse. Had two hemorrhages. Twitching of eyebrows and mouth. Tongue very dry.

October 17. Brighter and better in every way. After this he steadily improved, and left the hospital well on December 21.



CASE VI

CASE VI (Vol. lxxiv, Case 9773).—Female, aged fourteen years. Admitted September 13, 1911. Duration of illness, about twenty-six days. Very ill on admission. Tongue pale and moist, and covered with white fur. Abdomen distended. Remained ill and toxic during the next few days.

September 30. Had a restless night. Temperature, 103° to 104°; pulse, 124.

October 1. No marked abdominal distention. At 11 P.M. had rather profuse hemorrhage and again next day.

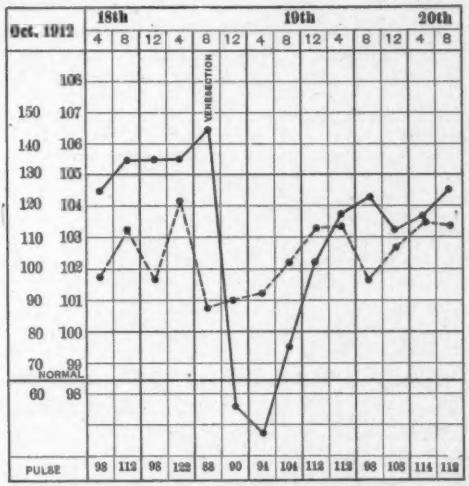
October 2. Abdomen distended. Involuntary urine. Later became worse and more toxic, with filling up of bases of lungs, and died October 5.

CASE VII (Not yet filed.).—Female, aged thirty-four years. Admitted October 17, 1912. Duration of illness, two weeks. Very toxic and paid no attention to surroundings. Lips dry and cracked. Tongue reddish brown. Spasmodic movement of chin. Hands tremulous. Abdomen distended and tympanitic. Spleen and liver palpable.

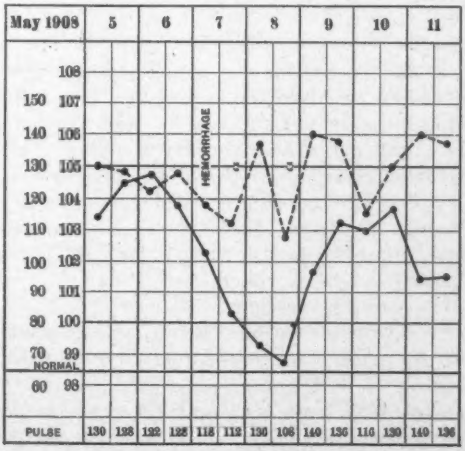
October 18. About the same. Seemed dazed, and at times picked at bedclothing. Temperature, 105°; pulse, 110. In the evening five ounces of blood were drawn off from median basilic vein of left arm and ten ounces of normal saline solution were injected into the vein. 6 P.M.: temperature, 106°; pulse, 130. Whisky, half an ounce, every four hours. Cold colon douche. Ice pack. Caffeine gr. 1, aspirin gr. 2, and acetanilide gr. ½, to be repeated in half an hour, and again in two hours if temperature did not lower.

October 19. 9 A.M.: temperature, 99°; pulse, 88. Listless and weak. Muttered at times. Tongue dry and reddish brown. Lips dry. After this she continued very ill, but less desperately so, and by the end of the month was much better and left the hospital well before the end of the year.

CASE VIII (Vol. xxv, Case 4210).—Female, aged thirty-two years. Admitted April 28, 1908. Duration, ten days. Was very ill on admission.



CASE VII



CASE VIII

May 1. Temperature high. Delirious and weak.

May 7. Hemorrhages early in morning and again at 1 P.M. Blood dark and not in large quantity. Abdomen much distended.

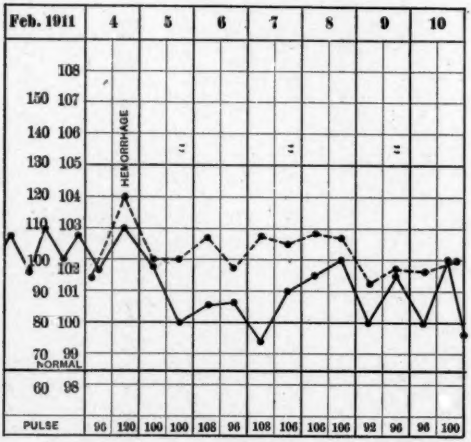
May 8. Another hemorrhage (slight) at 11.30. Distention still marked. A free hemorrhage at 6.15 P.M. Pulse much as before.

May 10. Pulse weak. Restless and unconscious most of time.

May 13. Marked improvement in last two days.

May 19. Weaker, and died at 5.15 A.M.

CASE IX (Vol. lxiii, Case 8870.).—Male, aged thirty-one years. Admitted January 19, 1911. Duration of illness, about nine days. Fairly well on admission. Was evidently near the end of the attack. Temperature, 100°, and was soon normal. A week later



CASE IX

had a relapse, and on February 4 a hemorrhage. On day before was dull and sleepy. Systolic blood pressure, 110. Slight bloating. Lips crusted and tongue red and beefy. Had another hemorrhage on February 5 and again on February 7 and 9. After that the patient steadily improved and left the hospital well on March 25.

CASE X (Vol. xxxi, Case 5145).—Male, aged twenty-two years. Admitted October 22, 1908. Had been ill for two weeks. Weak; sleepy; delirious; hard to arouse.

October 28. Had a hemorrhage.

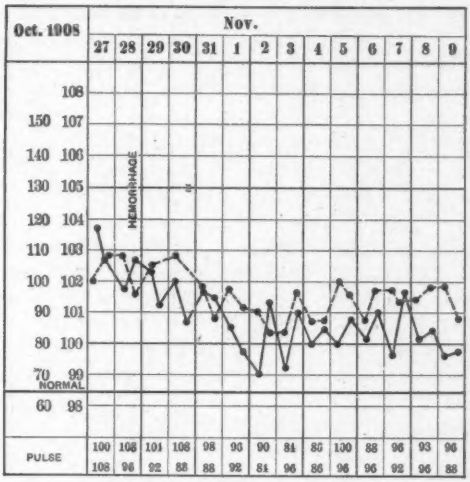
October 30. Had a hemorrhage.

November 1. Not so delirious; taking nourishment well.

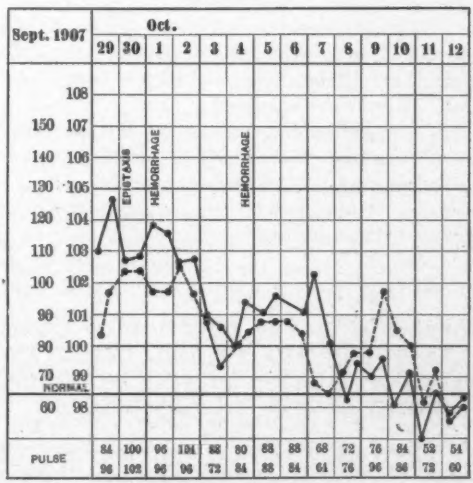
November 4. Able to speak. Recovered without further complications.

CASE XI (Vol. xviii, Case 3302).—Male, aged twenty-two years. Admitted September 23, 1907. Had been ill for three weeks when admitted; feeling better. Pulse showed marked dicrotism.

September 30. Epistaxis; feeling better.
October 1. Slight hemorrhage from bowel. Pulse and temperature not affected by it.



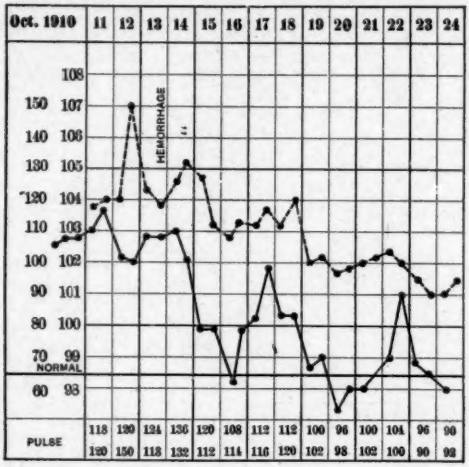
Case X



Case XI

October 4. Another slight hemorrhage.
October 5. Systolic blood pressure, 120.
October 10. Another epistaxis. Feeling well.
November 2. Discharged well.

CASE XII (Vol. lxiii, Case 8691).—Male, aged twenty-four years. Admitted September 19, 1910. Had been ill for four weeks. Very ill and drowsy; pallid; tongue dry and coated.



CASE XII

October 11. Nervous and trembling; very toxic; involuntary evacuations. Looked almost moribund. Drowsy and stupid. Lungs showed a consolidation at the right base. Extremely ill.

October 13. Very ill; profuse hemorrhage today.

October 14. More clots in stools.

October 15. Much better. Lung condition clearing. Pulse, 106 to 122; temperature, 98.2° to 99.2°. Had a good day, but did not rest so well during the night.

November 3. Doing well. Temperature and pulse normal. Was discharged well on November 27.

RECONSIDERATION OF THE QUESTION OF EXPERIMENTAL HYPERTROPHY OF THE THYROID GLAND, AND THE EFFECT OF EXCISION OF THIS ORGAN UPON OTHER OF THE DUCTLESS GLANDS.[1]

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THE space allotted is so short that I cannot do more than indicate in merest outline a few of the problems which have presented

[1] Read, by invitation, May 7, 1913, before the Association of American Physicians at the Ninth Triennial Session of the Congress of American Physicians and Surgeons.

themselves in the course of our study in animals and the human subject of the functions of some of the glands of internal secretion.

Twenty-five years ago, in the course of experiments upon the dog, undertaken chiefly with a view of determining the cause of death after operations upon the thyroid gland, I was surprised to find that excisions or transplantations or simple manipulations of the thyroid lobe were, after a time and almost invariably, followed by increase in the size of the remaining portions of the gland, wherever situated.

Examination of the hypertrophied tissue revealed the most unexpected and astonishing histological picture, a structure so different from the normal gland that not one of the several eminent pathologists in this country and abroad, to whom I showed the sections, was able to identify it. The histological changes which resemble those found in exophthalmic goitre are now so well known as not to require mention at this time. With few exceptions this hypertrophic picture made its appearance within twenty-two days after operation of any kind upon the thyroid gland, and even in its most advanced type was observed so late as ninety-five days after operation.

My observations have been confirmed by many, most carefully and convincingly by Marine, and the hypertrophy has generally been regarded as compensatory.

In my original article I expressed the view that possibly some form of auto-intoxication might account for the hypertrophic changes, and for some years have thought that the hyperplasia of the remaining thyroid tissue which has followed excision of a portion of the gland might possibly be due to infection of the wound, and for the following reasons:

1. The increase in the size of the remaining thyroids and the degree of hyperplasia as indicated by the histological picture seemed to bear no relation to the amount removed. The excision of so little as one-fourth of one lobe might be followed by great increase in the size of both lobes, and by the histological changes which characterize hyperplasia.

2. In 1888 I found that hypertrophy of the thyroid glands of dogs occurred after the injection of several cubic centimeters of a bouillon culture of Staphylococcus aureus into the peritoneal cavity, and also when a mild form of peritonitis had been produced in these animals—a peritonitis which was not rapidly fatal.

3. Experiments conducted in 1906 and 1907, in the Hunterian Laboratory, seemed to indicate that for the successful transplantation of a parathyroid glandule a considerable deficiency must be created.

4. Twice in the course of the past five years I have had opportunity to examine the remaining lobe of the thyroid gland after

excision of the other in dogs whose wounds had healed throughout without suppuration, and have noted that there was no hyperplasia of the former.

5. From a restudy of the report of my experiments on extirpation of the thyroid gland made in 1888, I find that for the major part of the experiments the wounds of the dogs were left open, and that after twenty-two days, with few exceptions, there was hypertrophy, macroscopic and microscopic, of the remaining gland in the animals whose wounds were permitted to heal by granulation, whereas when the wound healed *per primam* the hyperplasia of the remaining thyroid tissue developed perhaps less regularly and not to the same extent.

6. Manifestations of hyperthyroidism may develop promptly after tonsillitis, appendicitis, pneumonia, typhoid fever, and other infections.

In October, 1912, I proposed to Dr. Hunnicutt that he undertake a series of experiments with a view of determining the matter definitely. Observing aseptic precautions in the strictest manner, Dr. Hunnicutt has made a large number of experiments on dogs, and we are able to report that in none of the thyroids thus far examined has there been the slightest evidence of hyperplasia. The average time allowed to elapse between the removal of the first and second lobes was fifty-five days, the shortest interval being thirty and the longest eighty-one days.

That, nevertheless, there is such a thing as true compensatory hyperplasia of the thyroid gland is proved, I think, by my experiments in transplantation of the parathyroid glandules; which were conducted with the strictest aseptic precautions. Thus when both thyroid lobes and the four parathyroid glandules have been removed and only a film of thyroid transplanted with one parathyroid body, this film hypertrophies enormously, and on microscopic examination displays the typical changes of extreme hyperplasia. In one instance in which the graft was examined fifteen months after operation, the transplanted film had become as large as a good-sized pea.

If it should become a definitely established fact that true compensatory hyperplasia of the thyroid occurs only after the removal of a considerable part of this gland, and that infection or diet or some unknown factor has been responsible for most of the hypertrophies hitherto recorded, investigations are then made possible which could not be undertaken to any purpose if hyperplasia might be expected to follow operative interference of almost any sort upon the thyroid lobe.[2]

Although expecting that in wounds which healed by first intention

[2] In 5 unvaccinated dogs operated upon without precautions and whose wounds were left open, there was, greatly to my surprise, not the slightest indication of hypertrophy of the remaining lobe after thirty days.

hyperplasia might not develop after excision of small portions of one thyroid lobe, it surprised me to find from this year's experiments that so much as one and a half lobes may be removed without appreciable effect upon the remainder of the gland, and for the moment my interest in the search for an explanation of the entire absence of any sign of hypertrophy in the experiments of the past winter is as keen as it was years ago to explain the invariable hypertrophy which followed almost any sort of operative interference with the glandula thyroidea. Dr. Marine, replying a few days ago from Vienna to a letter in which I asked for his opinion, writes: "I am anxious to know whether you used iodine in the sterilization of the skin. This, as you know, inhibits to a marked degree compensatory hyperplasia following partial removal just as it does any physiological outgrowth. After trying all sorts of ways to check your 1888–1889 results we always got exactly what you then reported, and I shall have to have very conclusive evidence before being convinced that your results obtained in 1888 could be explained on the bases of wound infection." . . . "You have doubtless controlled the diet as a factor in compensatory hyperplasia."

In most of our experiments the skin has been disinfected with iodine, but in numerous instances it was not.

In 1888 our dogs were fed chiefly on raw meat, whereas during the past year their food has consisted almost exclusively of corn bread and cooked lungs of beeves. From the observations of David Marine, Reid Hunt, Chalmers Watson and others, which bear on this subject, it seems not unlikely that in the diet may be found the solution of the problem.

Should we find that, as a rule, three-fourths or more of the entire gland must be removed before the hyperplasic changes develop, this will be additional evidence to strengthen the belief that the thyroid gland is normally in a state of relative inactivity, and that it is an organ with great reserve power, capable of responding promptly, almost instantly, to certain stimuli.

Of particular interest in this connection are the experiments, just published, of Dr. Reich and Prof. Blauel, of Vienna. They find that in rats, whose thyroids normally have cuboidal epithelium, compression of the trachea is followed by flattening of this epithelium, to an extreme degree. If the oxygen-deprivation induced by the obturation of the trachea should prove to be the cause of the regressive or hypotrophic changes, might we expect to find that the colloid goitres which produce a great degree of tracheal stenosis are less likely to become Basedowified than those which are not accompanied by symptoms of suffocation?

Among the queries which present themselves at the moment are the following:

1. Must a deficiency be created for the successful grafting of ductless glands? Biedl claims to have successfully transplanted two parathyroid homografts in a dog which had not been deprived of any of its parathyroids. To justify his position, he states that all depends upon how long a transplant must live in order to be called a successful one. It seems to be an unchallenged proposition that a transplant cannot live unless it is functioning. But what is meant by functioning? Are tissues growing *in vitro* performing a function? Are the spirals of elastic tissue which we wind about the aorta functioning for a time? For about two months these spiral bands seem to live and continue to constrict the artery, but in six months they are almost absorbed.

2. What proportion of both thyroid lobes is it necessary to remove in order to produce hyperplasia of the remainder? The removal of one and one-half lobes has not been followed by hypertrophy in our experiments of this year.

3. Can a graft live without showing the hyperplastic picture? In other words, will a graft be absorbed unless the deficiency created is so great that hyperplasia must develop? Should the fact that a surviving graft retains the normal structure be taken as evidence that it will be absorbed (that its life will be short of duration)? And could a graft with such dubious existence be stimulated to hypertrophy and to prolonged life by the introduction of conditions which might demand of the thyroid increased function?

If we are still in doubt as to the cause of the hypertrophy of the thyroid glands in our experiments of twenty-five years ago, and are unable to explain its entire absence in our dogs of this past winter, after making scores of experiments to determine the effect of the removal of part of one gland on the remainder of the same organ, how infinitely greater are the difficulties incident to the explanation of the effects upon ductless glands other than the one surgically attacked.

Hypertrophy or enlargement of the hypophysis, for example, described by many authors as following thyroidectomy, has been observed in various parts of the gland: in the anterior lobe, in the pars intermedia, and even in the pars nervosa. There are conflicting views as to the changes which take place both as to situation and histological detail. By most investigators the formation of colloid is emphasized, and this has been interpreted by several as signifying a taking on by the hypophysis of the function of the thyroid; the colloid in the former replacing this substance lost in consequence of the thyroidectomy.

But when experimental hyperplasia of the thyroid takes place, the colloid, instead of being increased in the remaining hypertrophied lobe, is diminished or disappears altogether; and this being the case, it would seem strange that, after thyroidectomy,

it should appear in compensating fashion in the pituitary gland. We think of the normal thyroid, with its large follicles filled with colloid, relatively dense and deeply staining, as being in a state of comparative inactivity or rest; and the histological changes which have been stimulated in one gland by the removal of another have usually been considered as representing hyperactivity of this gland. But to me it appears unlikely that the colloid in the hypophysis which it is assumed makes its appearance in response to thyroid deficiency should signify hyperactivity of that organ, when the same colloid in the thyroid is found in abundance only in the comparatively inactive period of this gland.

It seems to be a natural inference that the loss of one gland of internal secretion should lead to the compensatory hypertrophy of another; and should colloid make its appearance in the eagerly observed unaccustomed places after the removal of a gland which normally is composed chiefly of colloid, the evidence for the compensatory nature of the change would seem to be so complete as to make further substantiation unnecessary. But I am quite sure that the evidence for the current view is not conclusive.

Is it not more probable that the elimination of the function of the thyroid may lessen, directly or indirectly, the demands on other of the ductless glands, and that the colloid changes noted in the hypophysis and parathyroids after thyroidectomy may signify hypo- and not hyperactivity of these organs?

A contribution by Kummer,[3] of Geneva, to the study of postoperative tetany, presented at the Twenty-fifth Session of the Congrès Française de Chirurgie, Paris, 1912, is worthy of unusual consideration. A women, completely deprived of the cervical thyroids and parathyroids, was kept alive for two years.

The autopsy was made by Prof. Askanzy,[4] who found in the hypophysis changes which seem to be identical with those described by William G. MacCallum[5] as having been present in the hypophysis of one of my dogs fifteen months after the removal of both

[3] Contribution à l'étude de la Tètanié postopératoire. Extrait des Comptes Rendus du 25e Congrès de l'association Francaise de Chir., 1912.

[4] Quotation from Askanzy: "*Hypophyse.* Les cellules chromophiles ou éosinophiles sont très abondamment développées, d'une richesse même extraordinaire. Par contre il n'y a pas d'augmentation de substance colloide dans les amas cellulaires de l'hypophyse, comme cela se voit dans les hypophyses chez les myxoedémateux. C'est seulement près de la partie nerveuse d'ailleurs intacte, dans la sone intermédiare soit médullaire, que l'on constate quelques follicules à substance colloide conformément à l'aspect ordinaire."

[5] Quotation from MacCallum: "The hypophysis shows rather distinct alterations. The pars nervosa is practically surrounded in the section by the pars intermedia which is perhaps slightly thickened and contains one or two alveoli full of colloid. The pars anterior is in part very deeply stained with eosin, but one portion, and that the major part, is sharply marked off from this eosin-stained tissue by its lilac color. It contains only a few of the bright staining cells, but for the most part is made up of swollen, faintly granular, pale stained cells. These resemble very closely the section obtained by Dr. Homans after injecting pilocarpin. The cleft in the glandular part of the hypophysis is here seen to open into the subarachnoid space." Halsted, Jour. of Exp. Med., 1912, xv, No. 3, 209.

thyroid lobes and of the four parathyroids. This dog, kept alive for this long period by a parathyroid autograft only 14 mm. in diameter, died of tetany on the removal of the transplant.

Rarely again should there be an opportunity to study on the human subject the effects, after two years, of the complete removal of the thyroid and parathyroid glands.

We have never observed hypertrophy of the transplanted parathyroids even when total thyroidectomy and total parathyroidectomy have been done. I am not prepared, at present, to report the results of operations to determine the effect, if any, upon the thyroid of excision of the parathyroids; but I am not quite willing to accept as proved the observations of others who claim that after thyroid lobectomy the parathyroids are stimulated to compensatory hypertrophy, forming follicles containing colloid. *Why should the excision of an amount of thyroid insufficient to bring about thyroid hyperplasia cause compensatory hyperplasia of the parathyroid glandules? And, granted that changes may have occurred in the glandules after thyroid lobectomy, should these consist in the formation of a colloid equivalent to the colloid of the thyroid alveolus if the thyroid-colloid disappears in cases of definite privation and if the accumulation of colloid seems to signify a state of normal or hypo- rather than of hyperactivity?*

Furthermore, if hypertrophy of the parathyroids really occurs after thyroidectomy, might it not be due to the unintentional destruction of some of the parathyroids, or even to infection of the wound? I have never observed hypertrophy of a transplanted parathyroid gland. The tendency of these grafts, in my experience, is always to atrophy.

An enormous amount of experimentation must be done before these questions, which are in no sense remote, can be answered. There are hundreds of eager workers in this fascinating field at present who may add immensely to the confusion, before, from the chaos, order eventually can emerge and the simple laws be established of which perhaps we are not even beginning to dream.

Hypertrophy of the thymus gland has frequently been observed in Graves' disease, and from our observations during the past ten or eleven years of a considerable number of such cases in which the greater part of both thyroid lobes has been removed, we think there is reason to believe that the thymus atrophies in consequence of the operation upon the thyroid. The lymphocytosis gradually disappears, and in none of the earlier cases which have presented themselves this past year for examination has the thymus been skiagraphically visible. It would seem, therefore, that the thymus may be activated by the thyroid.[6]

[6] Support to this view is given by the results of the experiments of A. L. Tatum reported since the reading of this paper (*vid.* Jour. Exp. Med., June 1, 1913). Tatum finds that in rabbits the thymus atrophies after excision of the thyroid gland.

AURICULAR FIBRILLATION: CLINICAL OBSERVATIONS ON PULSE DEFICIT, DIGITALIS, AND BLOOD PRESSURE.

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Recent studies with the electrocardiograph on animals under experimental conditions and on the human subject have permitted the separation of a group of cardiac irregularities known as "auricular fibrillation," which is of great clinical importance. So clear is the clinical picture of this group that in nearly ever instance the graphic records are unnecessary, and the ear and the finger are quite adequate to make a correct diagnosis. The clinical importance of this group is two-fold: (1) In it are included fully one-half of the serious cardiac irregularities which one sees, and (2) these are the cases which are almost invariably benefited by the administration of digitalis. A careful clinical study of a large number of cases of auricular fibrillation in hospital and private practice has prompted us to present the following points, which our experience has demonstrated to be of practical value in treating these patients intelligently and successfully.

The palpation of the radial pulse is a very insufficient criterion of the condition of the circulation. While the palpation of the pulse alone may be sufficient to establish a diagnosis, and while by this method one immediately detects the complete irregularity in force and frequency which characterize this group, the count of the radial pulse may be misleading. Frequently the number of the impulses which can be counted at the wrist is far below the actual number of cardiac contractions. Only those waves which are of considerable volume and force can be felt at the wrist, and many small ventricular contractions expend their force before reaching the radial, and some even fail to open the aortic valves. These small contractions are ineffectual in maintaining an adequate circulation, yet are exhausting to the heart muscle, for we know that, in accordance with the law discovered by Bowditch, every contraction of heart muscle is maximal: that is to say, if it contracts at all, it exhausts all of the energy stored as contractile material in its muscle fibers at any particular moment; hence it is evident that however small a contraction may be, it must be taken into

consideration in estimating the gravity of the condition of any particular heart.

The inadequacy of the observations on the radial pulse alone is well illustrated in Fig. 1. Here the lower margin of the shaded area indicates the radial count; if one were guided by this alone, one would have said that on admission the cardiac rate was under 70 and never above 100. The upper boundary of the shaded area is the count taken by auscultation at the apex, and represents much more accurately the true condition, the admission rate being 127; the gradual reduction to the neighborhood of 60 makes the real improvement apparent.

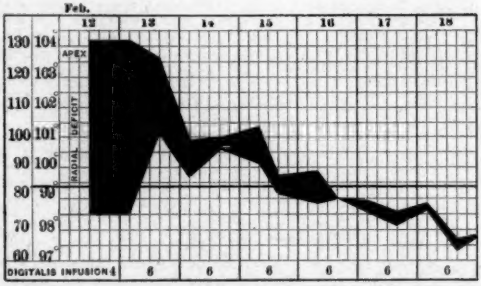

FIG. 1.—The shaded area represents the pulse deficit; the upper edge is the apex rate; the lower edge is the radial rate. Figures in digitalis column indicate dosage of the infusion in drams per twenty-four hours. Patient in bed during period represented in the figure.

The term "pulsus deficiens" has for a long time been used in describing pulse phenomena (Traube, Hering, Wenckebach, etc.), but each author has used it with a different meaning: some have considered it synonymous with "pulsus intermittens," others have applied it to an absence of ventricular contraction, which breaks the ordinary rhythm; it has been used in describing extrasystoles and pulse alternans.

So far as we know, Drs. Robinson and Draper, of the Rockefeller Institute, first used the term "pulse deficit" to designate the difference in the count when taken at the apex and in the carotid artery. *By "pulse deficit" we mean the difference between the number of cardiac contractions and the number of impulses which can be palpated in the radial artery.* The best way of determining the pulse deficit is to have the apex counted by auscultation by one observer while another is simultaneously counting the radial (these observations must cover a period of not less than a full minute, on account of the extreme irregularity of the pulse in many of these cases a count of one-quarter or one-half minute only is much less accurate). When one is obliged to make these observations unaided, the apex and the radial counts may be made

in sucessive minutes. This of course does not give an absolutely accurate deficit, but it is extraordinary how closely the counts of successive minutes will coincide even when the heart and radial show the most extreme degrees of irregularity. After a little practice one may be able simultaneously to auscultate the apex and palpate the radial, thus determining the number of beats which fail to reach the wrist in the period of a minute.

In the figures the upper margin of the shaded area represents the apex count, the lower margin the radial count, and the width of the shaded area represents the deficit at any particular point in the curve.

It is now generally recognized that the cases of auricular fibrillation are those which best respond to the administration of digitalis and drugs of this group. The mechanism by which digitalis acts in these cases is not entirely understood, but it is believed to have a direct influence in increasing the contractile power and tone of the ventricular musculature; besides this, it so affects the tissues junctional between the auricles and the ventricles that a portion of the irregular shower of impulses from the auricle are blocked, thus reducing the frequency of ventricular stimulation, allowing the ventricle to recover more completely, and to contract less frequently and with greater power. During each diastolic period thus lengthened the heart is better filled with blood which is more completely expelled during each systole.

The result of giving digitalis in these cases depends not so much on the form in which it is administered (tincture, extract, infusion, etc.) as on the amount and concentration of the active principles which each preparation contains. The effective method of its administration is to give enough of any particular preparation to obtain the physiological effect; the size of the dose necessary for any individual patient cannot be told in advance, but must be determined by its physiological effect in each case.

It is here, we believe, that a study of the "pulse deficit" is of great clinical value. A reduction in the degree of the deficit is the best indication of the effectiveness of the particular dose in the individual case.

When the deficit is abolished the digitalis must be discontinued or the dosage greatly diminished. Mackenzie, in his monograph on *Digitalis*[1] advocates the use of digitalis in auricular fibrillation until the physiological effects are evident. His method is to push the drug until the patient complains of nausea or until the characteristic coupled beats of the cardiac rhythm appear. Since we have been following our patients, guided by observations on the pulse deficit, we have usually been able to avoid the production of both nausea and the coupled beat, and while these symptoms occa-

[1] Heart, 1911, vol. ii, p. 278.

sionally appear, they are exceedingly rare. We are accustomed to continue the administration of digitalis as long as there is any considerable pulse deficit, and the dosage for the individual is so regulated that the pulse-rate is kept without deficit, and as near to 70 as possible. We have often given digitalis continuously in this way for a period of two years or over (see Fig. 3).

Another advantage of "pulse deficit" observations is the information it gives of the activity of any particular digitalis preparation; we have found it a simple method of making a physiological assay of particular preparations. If after a short period the "pulse deficit" is not diminished, we are apt to conclude that the preparation is inactive. As a rule, we have obtained the best results with an infusion, freshly made each day from the best English leaves.

The relative deficit. In many cases of auricular fibrillation, particularly where improvement has occurred and the heart has become less irregular, slow, and fairly compensated, it will be found that the count at the apex and the radial are identical. Even in these cases the individual waves show a considerable variation in force and size. This is brought more clearly to view if the cuff of a blood-pressure apparatus is placed on the arm and the radial is counted while varying degrees of pressure are applied through the cuff. This difference in the pressure values of successive waves we have termed the "relative deficit," as contrasted with the absolute deficit, when without brachial pressure some waves fail to reach the radial.

The following observation will serve to illustrate this point: The patient was a gentleman who had fibrillating auricles for something over two years, with at times an apex rate of 180 and an absolute deficit of over 50. His heart was fairly compensated, and he was able to supervise large business interests which required a daily attendance at his office of six to eight hours. When we last saw him his apex rate was 64, radial rate 64, deficit 0. On applying the brachial cuff the following counts were obtained:

Brachial pressure.	Radial count per minute.
140 mm.	0
130 mm.	50
120 mm.	58
110 mm.	62
100 mm.	64

While he had no absolute deficit, his relative deficit was quite evident when the pressure values of the waves of one minute were thus studied. This relative deficit may be detected in all cases of auricular fibrillation; it is rarely seen in other cardiac arrhythmias. We have found that such observations on the relative deficit are of real diagnostic value in corroborating a condition of auricular fibrillation which palpation and auscultation have led us to suspect.

The usual way of estimating *blood-pressure* is entirely fallacious in auricular fibrillation. The accustomed method of obliterating the brachial artery by cuff-pressure and then by gradually lowering the pressure to determine the systolic blood-pressure by the height of the mercury column at which the pulse wave below the cuff is detected by palpation or auscultation is obviously of little value when practically each pulse wave has a different pressure value. Mackenzie, in his recent monograph on *Digitalis*,[2] says "we gave up the attempt to register the blood-pressure in cases of auricular fibrillation, for though some sort of result could be obtained, the result would be expressed by a figure, and this would have given an aspect of precision, which it did not possess, and would therefore inevitably mislead."

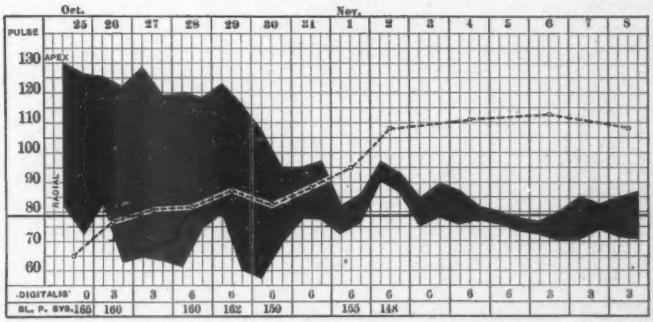

FIG. 2.—The shaded area represents the pulse deficit; the upper edge is the apex rate; the lower edge the radial rate; The broken line indicates the "average systolic blood-pressure" (compare these values with the figures at the bottom of the chart which show the systolic blood pressure determined by the usual method). Figures in the digitalis column indicate drams of the infusion per twenty-four hours.

If such a pulse is observed for a period of a minute it will be found that only a small fraction of the total number of cardiac contractions have a pressure value, approximately the systolic blood-pressure as determined by this method. Fig. 2 illustrates the inaccuracy of this method in these cases. Systolic blood-pressure taken by the usual method would signify that the successive blood-pressure of this patient were 165, 160, 160, 162, 150, 155, 148, etc., and that as her condition improved the blood-pressure was lowered. As a matter of fact, only a few beats could be detected below the cuff when exerting a pressure at these levels, and while doubtless her systolic blood-pressure was momentarily at these levels, they in no way indicate the efficient pressure of the blood column. As we shall show later, her systolic blood-pressure really increased with the improvement in her condition.

[2] Heart, 1911, vol. ii, p. 283.

A much more valuable estimate of the force of the blood-stream can be obtained by estimating the blood-pressure by another method; the average systolic blood-pressure.

To obtain what for convenience we have termed "*the average systolic blood-pressure*," the apex and radial are counted for one minute, then a blood-pressure cuff is applied to the arm, and the pressure raised until the radial pulse is completely obliterated; the pressure is then lowered 10 mm., and held at this point for one minute, while the radial pulse is counted; the pressure is again lowered 10 mm., and a second radial count is made; this count is repeated at intervals of 10 mm. lowered pressure until the cuff-pressure is insufficient to cut off any of the radial waves (between each estimation the pressure on the arm should be lowered to 0). From the figures thus obtained the average systolic blood-pressure is calculated by multiplying the number of radial beats by the pressures under which they came through, adding together these products and dividing their sum by the number of apex-beats per minute, the resulting figure is what we have called the "average systolic blood-pressure." The following two observations made on a patient will indicate the method of computation:

B. S., April 29, 1910. Apex, 131; radial, 101; deficit, 30.

Brachial pressure.	Radial count.
100 mm.	0
90 mm.	13 $13 \times 90 = 1170$
80 mm.	$47 - 13 = 34 \times 80 = 2720$
70 mm.	$75 - 47 = 28 \times 70 = 1960$
60 mm.	$82 - 75 = 7 \times 60 = 420$
50 mm	$101 - 82 = 19 \times 50 = 950$
	Apex = 131)7220
	Average systolic blood-pressure 55+

B. S., May 11, 1910. Apex, 79; radial, 72; deficit, 7.

Brachial pressure.	Radial count.
120 mm.	0
110 mm.	44 $44 \times 110 = 4840$
100 mm.	$64 - 44 = 20 \times 100 = 2000$
90 mm.	$72 - 64 = 8 \times 90 = 720$
	Apex = 79)7560
	Average systolic blood pressure 95+

The estimation of blood-pressure by this method gives us a simple and approximate measure of this factor of the heart's work. The diastolic pressure may be roughly determined by taking a graphic record with the Erlanger or Uskoff instruments and noting the pressure at which the average excursion of the pulse waves is maximal.

The effect of digitalis on blood-pressure in auriclar fibrillation. The effect of digitalis on blood-pressure has long been a matter

of contention. Thirty years ago it was thought that the administration of digitalis elevated blood-pressure, but this view was controverted by many subsequent observers such as Christeller, Fränkel, Heike, Hansen, Gross, Potain, and others. Their opinions have been summarized by Janeway,[3] who says: "All of the above observers fail to find any relation between the arterial tension and the circulatory improvement from digitalis."

Our present evidence justifies us in asserting that in the cases of cardiac insufficiency where digitalis is of most value, it raises blood pressure by slowing and increasing the force of ventricular activity.

The failure of former observers to recognize this fact was dependent on two elements: (1) that it was not then known that the benefits of digitalis administration are mainly evident in cases of auricular fibrillation, and (2) that they had no satisfactory method of estimating the blood pressure in these cases in which the successive contractions of the heart vary so greatly in force and time. Mackenzie says in his monograph on *Digitalis*, to which we have referred above, "In our observations, even when the drug was pushed and caused nausea and heart irregularities, we could detect no appreciable effect upon the blood pressure (except in one case)."

Since we have come to recognize that digitalis finds its chief usefulness in cases of auricular fibrillation, and have applied our method of estimating the average systolic blood-pressure to the study of this group, it has become clear to us that hand-in-hand with the improvement in the patient's condition the average systolic blood-pressure is elevated.

This is best made evident by the presentation of several charts, which have been selected from a considerable number, all of which show the same features.

Fig. 2 shows the effect of rest and digitalis on a case under observation in the Presbyterian Hospital for two weeks. The diminution in the deficit and the gradual increase in the average systolic blood-pressure is quite clear. During this period all of the patient's symptoms improved, and she was able to leave the hospital to return to her home.

This chart also shows how misleading would have been the systolic blood-pressure estimations made by the ordinary method (see figures at the bottom of the chart), for at these brachial pressures only four or five waves per minute reached the radial during the three days following her admission. The diagram indicates that the full digitalis effect is not obtained for four or five days; this we have found to be quite usual.

Fig. 3 is the chart of a gentleman who during the whole

[3] The Clinical Study of Blood-pressure, New York, 1904, p. 210

period of observation insisted upon following his ordinary occupation; he was not confined to bed at any time, although we should have considered this the wisest course when he was first seen. He therefore illustrates the effect of digitalis independent of the influence of any considerable amount of rest in the horizontal position. All the observations were made by one of us in his office. The rise in blood-pressure coincident with a slowing of the pulse and diminishing deficit and the fall of pressure corresponding to an increase in the pulse-rate and deficit stand out clearly. The observations cover a period of nineteen months, and the changes in the deficit and the blood-pressure could be closely correlated with his other symptoms. Whenever there was any considerable deficit or the blood-pressure fell this was associated with more or less dyspnea, a lack of vigor, and feelings of lassitude.

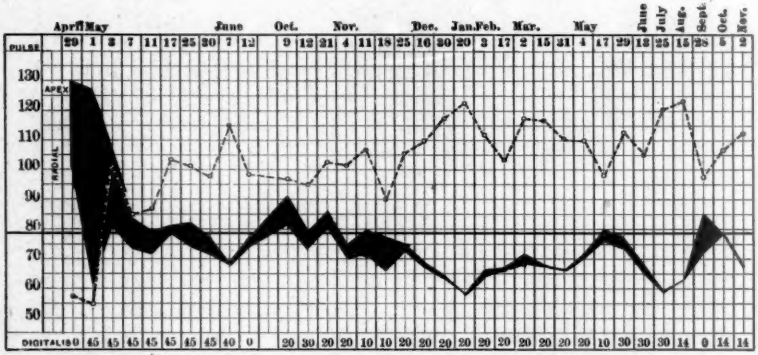

FIG. 3.—The shaded area represents the pulse deficit; the upper edge is the apex rate; the lower edge the radial rate. The broken line is the "average systolic blood pressure." The figures in the digitalis column indicate minims of the tincture per day. Patient not confined to bed.

Fig. 4 is that of a woman who was in the Presbyterian Hospital during the whole period of observation as represented by the diagram. The initial deficit on admission, which showed a marked and sudden diminution with the administration of a freshly made infusion of digitalis (an ounce was given on October 17), the first setback induced by getting out of bed, her subsequent improvement under rest and digitalis, the second setback brought on by an attack of hemorrhoids and the variations in blood-pressure associated with the various stages of her progress, are all indicated in a graphic manner. Unfortunately the blood-pressure observations are not as numerous as one would wish, but the inverse relationship between the average systolic blood-pressure and the pulse-rate and deficit are evident. It is difficult to analyze the last setback, as three elements took part in its production: (1)

the upright position, (2) the withdrawal of digitalis, and (3) the pain attendant on the attack of hemorrhoids and their incision under cocaine. It seems resonably evident, however, when we compare this with the preceding setback, that the hemorroidal discomfort was a considerable factor in aggravating the circulatory deficiency.

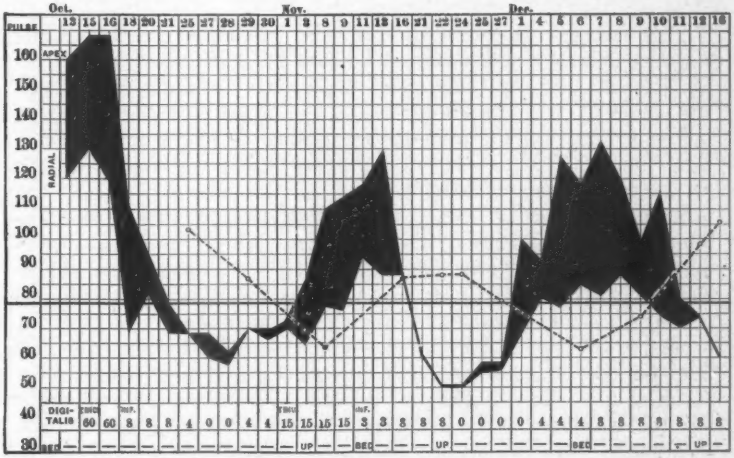

FIG. 4.—The shaded area represents the pulse deficit; the upper edge is the apex rate; the lower edge is the radial rate. The broken line indicates the range of the "average systolic blood pressure." Digitalis figures indicate minims of the tincture and drams of the infusion. October 13, admitted to hospital. November 3, up in chair one-half hour; November 9, up in chair two hours. December 4, up in chair four hours; at this time she had a crop of external hemorrhoids which caused much distress.

CONCULSIONS. 1. In auricular fibrillation palpation of the radial pulse is a misleading guide to the determination of the condition of the circulation.

2. The pulse deficit is a simple and useful means of following the progress of cases of auricular fibrillation, and of confirming observations on the value of various therapeutic measures, including the activity of various preparations of different drugs.

3. The relative deficit is of value in the diagnosis of suspected cases of fibrillation.

4. The ordinary method of estimating blood-pressure is misleading in cases of auricular fibrillation; it may with advantage be replaced by estimating the average systolic blood-pressure, which gives an approximate measure of the real systolic pressure.

5. The administration of digitalis elevates blood-pressure in cases of auricular fibrillation.

THE MINUTE CHANGES PRODUCED IN LEUKEMIC TISSUES BY EXPOSURE TO RÖNTGEN RAYS.[1]

By Aldred Scott Warthin, Ph.D., M.D.,

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(From the Pathological Laboratory, Ann Arbor, Michigan.)

The changes produced by Röntgen irradiation in the blood-forming organs of experimental animals have been fully described by Heineke, myself, and other observers. In previous reports[2] the writer has also described the changes produced in the tissues of leukemic patients by prolonged exposure to these rays. Since that time he has had additional opportunities of examining the tissues of leukemic cases treated in this manner. in all the autopsy material of eight cases of myelemia, two of lymphemia, three of Hodgkin's disease, and a number of lymph nodes and spleens taken from such cases. These cases present, therefore, a varied range insofar as the period of irradiation is concerned; in some, the tissues show the early action of the rays; in others, the changes are those produced by irradiation extended over periods of one year, eighteen months, and two years. As a result of this study, it has been possible to separate the immediate and remote effects of the irradiation, and to distinguish the changes so produced into two classes: *immediate* or *degenerative* and *reactive*. A number of interesting observations have been made during the investigation, and it seems worth while to present here in condensed form the total results of these observations.

The immediate action of Röntgen rays upon the tissues of leukemia is a degenerative one. Cells are either killed outright or are so damaged that they die within a short period, both cell body and nucleus showing rather specific changes, so that it is possible to distinguish these degenerative changes from those produced in leukemic tissues by infections or other injurious agents. The cells so injured are the small and large lymphocytes, myelocytes, myeloblasts, large lymphocytes, and to some extent, also, the polynuclears. After a prolonged period of irradiation there comes an apparent period of adjustment to this destruction, the tissues contain fewer evidences of cell death and degeneration, but also fewer proliferating cells. In the blood-stream the number of white cells may decrease to normal or below normal; but it may, on the other hand, steadily rise until the number is much greater than before the irradiation, that is, a leukemic condition of the blood may be reduced to an aleukemic under the progress of the treatment or

[1] Presented before the Section of General Pathology, XVII International Congress of Medicine, London, August, 1913.

[2] International Clinics, 1906; Trans. Amer. Röntgen Ray Soc., 1906.

the reverse may take place. In the cases dying after prolonged treatment with Röntgen rays the character of the cells in the spleen, lymph nodes, and bone-marrow is different from that of these organs in patients who have received no Röntgen-ray treatment. Upon these differences we base our description as follows:

I. Degenerative Changes. As the result of single exposures, or of several within a relatively short period of time, the tissues of the lymph nodes, spleen, and bone-marrow, in the order given, show patches of degenerating cells, as manifested by nuclear fragmentation and swelling of the celll. In the earliest cases the nuclear membrane of the cells (lymphocyte, myelocyte, etc.) is preserved, the nucleus swollen, with fragmentation of its chromatin, into spherical granules of varying size. The protoplasm may show no changes or become clearer, often vacuolated. The cell so damaged does not show these changes immediately after the irradiation, but usually within ten to fourteen days. The injured cells then rapidly split up into fragments, all traces of the protoplasm are lost, and only the chromatin granules remain, often as "chromatin dust." This injury to the cell is not a diffuse one; apparently only certain cells are affected, as many cells apparently normal are found near the degenerating cells. In the lymph nodes the degenerating cells may be found especially in the germ centres if these are still preserved, but after a time they are found all thorough the node. Repeated exposures cause an increase in the number of the degenerating cells, the greater part of the gland may become necrotic, in some glands all cells may be killed, and a caseous detritus finally takes the place of the cells of the node, the connective-tissue capsule gradually becoming thicker. These changes are more marked in the lymph nodes of Hodgkin's disease and lymphemia than in those of myelemia. In the spleen the reverse is apparently true; the myelemic spleen shows greater cell-degeneration and cell-necrosis than does the lymphemic spleen. The atypical myeloid cells in this condition suffer chiefly, especially the large bone-marrow lymphocytes, or myeloblasts. The myelocytes and cells of the type of bone-marrow giant cells also are easily killed and disappear, until finally all atypical myeloid cells in the spleen may be entirely absent, and the spleen appear as a fibroid organ containing scattered lymphoid cells. The reduction in size of the myelemic spleen may, therefore, be considerable, and in our experience is always greater than that of the lymphemic spleen. Similar degenerative changes occur in the bone-marrow, but are less marked. It is much more apparent in myelemia than in lymphemia.

Lymph nodes removed some months after continued irradiation for short periods daily show in lymphemia and Hodgkin's disease many large cells containing a diffusely staining or granular protoplasm. Areas of cells containing numerous fat droplets begin to appear, and finally the nodes may contain large areas of fatty

degeneration. The vacuolated cells may ultimately go to pieces and large fat droplets remain in the tissue detritus. Cholesterin crystals soon form in these, so that it is not uncommon to find in the irradiated glands of lymphemia and Hodgkin's disease areas of caseation containing fat droplets and cholesterin clefts. Even under the continued irradiation, foreign-body giant cells may develop in these areas. In some glands all of the cells finally assume the type of large, pale lymphocytes, with vacuolated protoplasm. The writer has never found these fatty changes in the lymph nodes of myelemic cases.

In the blood-smears made from myelemic and lymphemic patients the reduction in the number of white cells with a great increase in the number of degenerating forms are the chief changes observable. The reduction in lymphemia is not as striking as it is in myelemia; on the contrary, the number of small lymphocytes in the blood may steadily rise in spite of the irradiation; and in one case of Hodgkin's disease irradiated over a long period of time, the blood which showed no leukemic characteristics at the beginning of the irradiation gradually took on the characteristics of a lymphatic leukemia, with great numbers of large lymphocytes in the circulating blood. There is apparently a limit to the degenerative action upon the white cells and blood-forming organs during irradiation; and after a certain time some adjustment or reaction to the irradiation apparently takes place.

II. Reactive Changes. The reactive changes are shown by a diminution in the number of degenerating and necrotic cells in the blood-forming organs, and in a change in the type of cells forming the bulk of these tissues. In lymphemia and Hodgkin's disease the reaction takes place much more quickly than in myelemia. Around the necrotic glands in the first-named condition there is regenerated a new and atypical lymphoid tissue characterized by a great number of atypical large lymphocytes, of a character resembling the maternal lymphocytes of hyperplastic germ centres, seen in chronic inflammations of the tonsils and other lymphoid tissues. These cells have a granular cytoplasm, staining more heavily with eosin and hematoxylin, and with granular nuclei. This newly formed atypical lymphoid tissue may infiltrate the capsule of the lymph node and extend into the necrotic area, replacing it in part; or if it begins within the lymph node it may infiltrate through the capsule into the surrounding tissues. New areas of atypical lymphoid tissue develop in the cervical, axillary, and prevertebral adipose tissue. In these new areas vacuolated cells are very common, as are also large, pale cells of endothelial type. Collections of hyperchromatic cells with large irregular nuclei occur throughout this new tissue. In the lymph- and bloodvessels of this tissue there is a great increase in cells of the atypical lymphocyte character.

In the case of myelemia treated over long periods of time the peripheral lymph nodes may show at death little change except a poverty in germ centres and an absence of cells of the bone-marrow group. The retroperitoneal hemolymph nodes may show a marked hyperplasia of atypical cells resembling the large lymphocytes of the bone-marrow. All distinction between the cords and trabeculæ and sinuses is lost; the entire gland is made up of densely packed cells that infiltrate through the capsule and into the neighboring fat tissue. The bloodvessels may or may not show any increase in the number of white cells, but usually contain cells of the large lymphocyte type. No other cells of the bone-marrow group are found in these hyperplastic prevertebral glands. I have not found in my cases as marked an atypical regeneration of leukoblastic tissue in the spleen as in these glands. In some cases the spleen is fibroid to the end, with few or no cells that can be regarded as myeloid in type. In two cases large areas of caseous necrosis, hemorrhages, and anemic infactions, associated with thrombosis of the splenic vessels, were present. One case showing these changes in a marked degree died from a rupture of a splenic artery, the spleen at autopsy being embedded in a large clot proceeding from a small opening in the capsule of the organ communicating with a small-sized artery. The arteries of the spleen showed an obliterating endarteritis, and the majority of the smaller vessels were thrombosed. No myeloid tissue was present in the organ, although the other organs of the body presented the usual appearances of leukemia.

The changes in the bone-marrow resemble those in the retroperitoneal hemolymph nodes in those cases in which the leukemic condition of the blood had changed to an aleukemic under the treatment. Cells of myeloid type were present in greater numbers, but the chief cell of the marrow was the large pale lymphocyte (myeloblast?). In no case treated by Röntgen irradiation were the conditions in the hematopoietic organs changed to a normal condition. The effect of the treatment is essentially degenerative and inhibitive, but the essential leukemic process goes on unchecked, although greatly modified. The treatment is, therefore, not curative; and such a result we no longer expect from our clinical failures.

In the first stages of the treatment the leukemic tissues show great degeneration and destruction of the white-cell-forming tissues. It may completely disappear from the spleen, and the processes of white-cell formation may be so inhibited that an aleukemic condition of the blood may result. After some months there arises a more undifferentiated leukoblastic tissue, particularly in the retroperitoneal hemolymph nodes and in the bone-marrow; the leukemic condition of the blood may return or it may not. With an increasing cachexia the process may be terminated by symptoms of intoxication, or by some secondary event, as hemor-

rhage from the necrotic spleen. The changes in the kidney, which may be very marked (cloudy swelling, simple necrosis, and calcification), may also in part be responsible for the fatal termination.

In conclusion, prolonged irradiation of the hematopoietic organs in leukemia causes first a degeneration of the young and maternal cells, leading to a great decrease in the output of leukocytes, particularly in myelemia. To this destructive effect there follows a reaction in which cells of a more resistant type are formed, and the essential leukemic process remains unchecked, although altered in character.

CAN IT BE PROVED FROM CLINICAL AND PATHOLOGICAL RECORDS THAT THE NUMBER OF CURES OF CANCER WILL BE GREATLY INCREASED BY THE PROPER EXCISION IN THE EARLIEST PRECANCEROUS OR CANCEROUS STAGE OF THE LOCAL DISEASE?[1]

By Joseph Colt Bloodgood, M.D.,

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Clinical evidence has gradually accumulated which demonstrates that we can increase the number of cures of malignant tumors.

This evidence has been slow in accumulating, due to many factors. In the first place, patients have sought advice late; both surgeons and physicians in the past have delayed action until the diagnosis of malignancy had become obvious clinically.

In the beginning of surgery of neoplastic lesions the operation, except amputation for sarcoma, was not radical enough, and unfortunately amputation for sarcoma rarely cured the truly malignant tumor, because in these cases metastases take place early, before the local symptoms are sufficiently grave to influence the patient to consent to amputation or to force the surgeon to this mutilating operation.

Resection of the stomach for cancer by Billroth was perhaps the beginning of radical operations for malignant disease followed later by the complete operation for cancer of the breast (Halsted's method, 1889). The better results of the latter operation as compared with simple removal of the breast for cancer were soon known.

As surgeons have operated more radically and as patients have sought advice earlier the number of cures of cancer and sarcoma has increased.

In the past a radical operation was spectacular, bloody, involved

[1] Read before the American Association for Cancer Research, Washington, D. C., May, 1913.

great risk to life, and often mutilated. But when these operations were performed for malignant disease in the later stages they were not really radical, because the disease was rarely, if ever, completely removed.

Today the word "complete" is a better term for the proper operation for malignant tumors.

In the surgical pathological laboratory of the Johns Hopkins Hospital we have kept complete records of all cases from which pathological material was obtained for histological examination. In the majority of these cases we still have the tissue and the sections. The ultimate results have been ascertained from time to time, the old sections restudied, and new sections made from old blocks for reinvestigation.

It is upon the evidence of this investigation, which has been going on for more than five years, on material collected for more than twenty years, that the statement can be made that the number of cures of cancer can be increased.

Benign Pigmented Moles. This is rather a distinct type of tumor, clinically and histologically. The mole is undoubtedly of embryonic origin; whether the cells are of epiblastic or mesoblastic source makes practically little difference. For years physicians and surgeons have been familiar with the malignant tumor which may develop in one of these innocent moles at any time of life, usually late—after forty years. In the past, surgeons have again and again operated for the malignant development, or at least for what they considered malignant change; that is, local growth in the mole with slight ulceration. After such operations the patient usually returned with metastases and was sometimes subjected to operation again. Due to the unfortunate fact that, until recently, careful investigation of the ultimate results were not made, the hopelessness of this malignant pigmented mole has only been appreciated in recent years. The writer has records of 68 cases; in 43 of these there is no question but that the malignant tumor developed in a congenital pigmented mole; in the remaining 25 cases the patient was unaware of a congenital mole, but had observed a mole, not at all different from a congenital mole, months or years before the beginning of the symptoms of the malignant growth. In this group of patients there is but one which may be considered as a possible cure. The specimens in this case were sent to me by Dr. Wainwright, of Scranton, Pa., and there can be no doubt as to the clinical and pathological malignancy. In addition to the operation for the primary tumor, two operations were performed for metastatic tumors. Microscopically, the three pieces of tissue show the typical pigmented alveolar tumor, which I prefer to call malignant pigmented mole.

During this same time we have records in the laboratory of 175 benign pigmented moles, the majority congenital, some first ob-

served later in life. In the beginning of the history of this clinic only the larger pigmented moles were removed, so that in the first ten years of the life of our records the number of the malignant pigmented moles was greater than of the benign. In the past ten years it has been the rule to remove the benign moles whenever an opportunity was given, with the sole object of protecting the individual from the possible development of the malignant lesion which in the majority of cases is fatal.

I am unable to find among the benign pigmented moles so removed a single instance of later malignancy, in the scar or elsewhere. This shows that the histological examinations and diagnoses combined with the clinical picture were accurate. This shows, also, that there is no danger from the excision of a benign pigmented mole. However, again and again, when I have discussed this in public addresses, some one or more present have made the statement that it is dangerous to cut out a pigmented mole; that there is usually local recurrence in the scar; and not infrequently secondary development of malignancy. I have never observed such a result in any of our cases where the excision had been complete.

Here, therefore, is a pure clinical and pathological investigation, a complete record of the disease demonstrating that the number of cures of the malignant pigmented mole can be increased only by educating the people and the profession to the possible potential dangers of the benign pigmented mole. A chapter could be written on what moles should always be removed and on the more dangerous situations, but this is not the place for this presentation. We require no better proof of the value of a painstaking and accurate investigation of the ultimate results in a large number of cases of a single type of malignant tumor and its benign prototype.

Benign Connective-tissue Tumors. I have for comparison 406 cases of benign connective-tissue tumors of the skin and subcutaneous tissue with 132 examples of sarcoma. This shows that the probability of malignancy is at least 25 per cent. It is quite true that patients suffering with the different types of benign connective-tissue tumors, who have delayed treatment for months or years, have not suffered, except in rare instances, for this delay. It may, however, be stated emphatically that every one of these patients ran the risk of sarcoma developing in the benign tumor. These benign connective-tissue lesions are visible and palpable. In many cases the diagnosis is positive from the clinical picture only—for example, in hemangioma of the skin. Others are subcutaneous masses, and their nature can only be suspected. In the past, both surgeons and physicians have viewed these benign connective-tissue tumors lightly, and unless the patients have sought advice on account of the increasing size and discomfort of the tumor, operations have not been advised. During the

same time surgeons have been operating upon and saving very few sarcomas. The writer does not know whether they have realized the high mortality of sarcoma of the skin and soft parts, or that when these cases of sarcoma come under their observation the tumor had usually been present a year or more, and that in the beginning the lesion, with great probability, had been one of the various types of benign connective-tissue tumors.

The second neglected clinical fact is trauma. The swelling so common after contusions receives little attention, unless it causes great pain. A swelling which does not disappear after a certain time, or which reappears after a certain period, is a significant clinical phenomenon usually not appreciated until too late, when sarcoma has become clinically evident, and the probability of a cure least. The number of inoperable cases is large.

The following figures in regard to sarcoma of the skin and soft parts illustrate these points.

Sarcoma of the Skin. In 6 cases the perithelial angiosarcoma developed in a congenital nevus. The local growth in the nevus had been present for years in all cases before the patient sought operative help. There had been an opportunity in every case to excise the congenital nevus locally the moment these local changes took place. Among these 6 cases only 1 cure is recorded.

In 8 cases of sarcoma of the skin the tumors, macroscopically and microscopically, could not be differentiated from the 6 cases of perithelial angiosarcoma which developed in congenital nevi. In 5 of these cases the tumor had been present one or more years in only 3 cases less than a year. In every instance, therefore, there had been an opportunity for an earlier complete local operation. Not one of these 8 cases was cured.

The writer has records of 95 cases of hemangioma of the skin and subcutaneous tissue; 15 fibroangiomas; 13 granulation-tissue tumors; 9 intermuscular angiomas—132 benign tumors, therefore, as compared with 14 sarcomas of the skin. These 132 patients with benign angiomas had, as a matter of fact, nothing to gain by delay. The probability of malignant degeneration is comparatively slight, but the probabliity of multilating growth is so great that there is every reason not to delay in the treatment of an angioma.

20 cases of sarcoma of the skin developed in scars. In this group there are 8 cures; 7 patients, we know, are not cured; 5 patients have been lost track of. In every one of these cases the growth in the scar had continued one or more years, so that in every case there was sufficient clinical indication for an earlier intervention. Now, if the probability of a cure be 50 per cent. in late intervention, we can be quite sure that it will be much greater in early intervention. These scar-tissue sarcomas are entirely different local growths from the benign keloids, of which we have 49 examples,

We cannot enter here into a discussion of the difference between the benign keloid and the other fibrous growth in scar tissue, which is more dangerous. The malignant tumor is more apt to develop in the scar the seat of an ulcer.

In 9 cases of sarcoma of the skin there was a distinct history of a fibroma: 5 of these cases have been cured; 3 we know were not cured, but died of metastastic sarcoma. In every instance the original tumor—the fibroma—had been present one or more years. The clinical changes which suggested malignancy were rapid growth, infiltration of the covering skin or epidermis, and superficial ulceration. One, however, cannot prognosticate from this local growth the malignancy of the tumor. One of the cured cases was clinically most malignant, one of the cases which died of metastasis least so.

During the same time we have records of 67 cases of benign fibromas: 20 of these were situated on tendon sheaths, 13 in the abdominal wall, and 34 were either subepidermal or subcutaneous. From these figures, therefore, the probability of malignant degeneration in a fibroma was 13 per cent.

As far as we know multiple sarcoma of the skin and mycosis fungoides are incurable diseases, but the precancerous lesion of the skin, whether it be of epithelial or connective-tissue origin, is so distinct that our future statistics should show a great decrease in the number of malignant tumors and a correspondingly greater increase in the number of the precancerous benign lesions. I feel that a patient with a sarcoma in a scar or in a fibroma should always be treated in time for a cure. The rapid development of some of the perithelial angiosarcomas of the skin shows the danger of even a short delay. For example, in this group there are 3 tumors of the scalp, single tumors which clinically could not be distinguished from benign wens. Yet, after their removal, they proved to be sarcoma, and the patients died of metastases.

Sarcoma of the Soft Parts. The proof of a distinct precancerous lesion in this group is more difficult, but in the great majority of cases some palpable lesion had been present at least a year —long enough, therefore, to justify exploration.

In the fibrospindle-celled tumors, which resemble sarcoma of the skin developing in a scar or fibroma, we have but 3 cures among 8 cases; in only 3 of these cases had the lesion been present less than one year.

The fibromyxosarcoma of nerve sheaths is a distinct clinical and histological lesion. They may be single or multiple. In many instances the little tumor is observed at birth, in others it appears later in life. Our records show 32 examples of benign fibromyxomas of the nerve sheaths; in 9 instances the lesion was multiple; in 11 cases the removed tumor was in places histologically sarcoma; in 3 of these cases the patients had multiple tumors, one of which,

however, showed growth and malignancy. Of the 9 traced cases only 4—less than 50 per cent, have remained well; 5 patients died of local recurrence or internal metastasis. In 9 of these 11 malignant cases the tumors had been present one year or more.

The remaining cases of sarcoma of the soft parts belong to the most malignant type. There are 63 cases in all: 11, or 17 per cent., were inoperable. In not a single one of these 63 cases was the palpable mass subjected to operation within one month. In 34 cases the tumors were present one year or more; in 29 cases one month to one year. Among these 63 cases there were but 5 cures. The failure to cure was due in many instances not to the extent of the local growth but to metastases. Many of these patients gave a history of trauma previous to the appearance of the lump. Five cures are less than 8 per cent. These tumors were all cellular sarcomas of different types. Among the 10 cases of endothelioma there were two which developed in subcutaneous tumors, these had been present ten and twenty years. These little, innocent, compressible, palpable nodules could have been easily removed during the years of quiescence.

Few in the profession know how relatively few the cures are in sarcoma. Here we have 84 cases of the skin and soft parts with but 13 cures, or 15 per cent.; in the less malignant type 21 cases with 9 cures, or 42 per cent.; in the more malignant type, 63 cases with 5 cures, or less than 8 per cent.

There is no way to increase the number of cures in this type of malignant tumor except by educating the people and ourselves to the radical removal of skin and subcutaneous nodules the moment they appear. Such operations need never be multilating nor dangerous. Intervention for the swelling after a trauma must also be resorted to early.

These, therefore, are our statistics of benign and connective-tissue tumors which indicate what a clinical investigation can do toward the improvement of the results in the treatment of malignant disease.

Epithelial Tumors. Here we have for study 977 cases of epithelial tumors of the skin and visible mucous membrane which have been subdivided into the following localizations: lower and upper lip, face, chin, eyelid, ear, nose, scalp, mucous membrane of the gum and mouth, tonsil and pharynx, larynx, tongue and floor of the mouth, skin of the neck, branchial cleft cancer, skin of the upper and lower extremities, penis and body. In every one of these cases the cancer had developed in a preëxisting lesion. Up to the present time only 173 individuals presented themselves for treatment with benign lesions, or 17 per cent. We have been unable to find a single local recurrence or death from cancer in this group. The benign lesions had been warts of various types, areas of keratosis of various types, and benign ulcers. It is inter-

esting to note that the number of these benign lesions applying for treatment are on the increase. Up until 1910 the percentage of these was but 14, in the past two years the benign precancerous lesions have increased to 39 per cent., and the relative number of fully developed cancer is apparently on the decrease. Of course, this is difficult to estimate with any degree of accuracy until the difference is more marked; 69 cases, or 8 per cent., came under treatment as warts, that is, clinically benign lesions; but when studied microscopically they proved to be malignant. In this group up to the present time we have been able to find but one failure to cure. In this case the warty growth on the lower lip extended almost from angle to angle of the mouth, and we feel convinced that it was incompletely removed. The failure to cure, therefore, was due to the operation. In the remaining cases the skin lesion was fully developed carcinoma. We mean by this in the gross an ulcer or a fungus, and microscopically a carcinoma. We can recognize three distinct types: the *basocellular carcinoma*, 19 per cent. of the total cases, with the probability of a cure in 70 per cent. from our experience; this includes all cases—inoperable, extensive, and recurrent. The *carcinoma spinocellulare* is the most frequent type of cancer. The large number of this type of cancer is due to its common occurrence on the lower lip and tongue, and here the spinocellular cancer predominates. Considering all cases, the percentage of cures in this group is 40. There is a third type of carcinoma of the skin and mucous membranes, one in which the tumor is composed of transitional epithelial cells. Krompecher employs for this form the term *carcinoma cubocellulare*. These cases represent but 5 per cent. of the total, and the percentage of cures is 33.

In an experience, therefore, of more than twenty years with 820 cases of malignant tumors of the skin and mucous membranes, the percentage of cures varies from 33 to 98 in the four types of cancer. We feel certain that this number of cures should be greatly increased, in some localizations, to even 100 per cent.

My table shows that between the years 1890 and 1913, 16 patients have sought advice with lesions of less than one month's duration. (Practically all of these are recent cases, and in people who have been reached directly by the education of the students of the third and fourth year.) Fifty patients sought advice within two months after the onset of the first lesion; 77 between three and six months; 109 between six and twelve months; 344 one to ten years or more. In many cases we have no exact data.

In epithelial tumors the danger of delay after the first symptoms varies with the character of the lesion and its localization. In some localizations one day's delay is equal to a week in another, a month in still another, and a year in still others. The danger of delay is greatest in the spinocellular tumors and in localizations, such as the lower lip and tongue.

It is hoped that these statistical figures of clinical, pathological, and ultimate-result records will prove that the number of cures of cancer will be greatly increased by the proper excision of the precancerous lesion or of the malignant lesion in its earlier stage, and there is no reason why this should not be done. No one is ignorant of the lesion in its early days, they are only ignorant of its potential dangers. To cut out with the knife these lesions in their earliest stages is not major surgery, but it is delicate surgery. The surgery presents no danger, rarely much discomfort, and seldom even slight mutilation. But the surgeon must know how to cut out these lesions. To leave a piece of the benign wart, or of any other type of precancerous lesion behind, is to leave a focus more dangerous than the entire focus uninjured. To incompletely cut out cancer in its earlier stages gives worse results than a complete eradication later.

The danger of excision of the precancerous or early malignant lesion is due to the fact that the surgeon may make his operation less complete because of the innocent appearance of the lesion. There is absolutely no necessity for this. In some cases, especially in the early malignant stage, the Paquelin or electric cautery, or fulguration, may be employed with or without the knife, but a piece of the lesion should always be obtained for microscopic record. Otherwise we will have no check and no accurate knowledge of what we are treating. In a few cases the clinical evidence of malignancy is so obvious, the danger of cutting out a piece so great, and the situation of the lesion so convenient for cautery or fulguration, that we treat the disease without microscopic proof. But this is a strictly surgical problem.

We are also confident that we shall be able to show in a future article that the number of cures of cancer in the later stages can be increased by better surgery.

We have discussed here the problem of lesions of the breast, of the jaws, thyroid and salivary glands, the stomach, gall-bladder, colon, or rectum, but here too our material and the clinical, pathological, and ultimate-result records will show that the number of cures of cancer will be greatly increased by the proper excision of the precancerous lesion or early cancerous stage, and that better surgery will increase the number of cures even in the later stages of cancer.

Surgery at the present time offers more for the cure of cancer than any other method of treatment, and is doing more today than merely treating cases of cancer as they apply for help. Surgeons are collecting these statistics, by which they hope to educate the people that incurable cancer is, in the great majority of cases, a preventable disease. All that patients are asked to do is to submit to an operation in the beginning of the trouble, and this operation should excite no fear or anxiety.

NOTE.—Since this paper was written, the results in all the cases of carcinoma and sarcoma have been again ascertained during the past summer. I will give here the results, as roughly computed, in the cases of cancer of the tongue, lip, and breast. These results add confirmation to the evidence already offered—that it can be proved from clinical and pathological records that the number of cures of cancer will be greatly increased by the proper excision in the earliest precancerous and cancerous stage of the local disease. These figures are based on cases recorded in the surgical pathological laboratory of the Johns Hopkins Hospital. Most of the tissues and records in these cases have come from the clinic of Prof. Halsted, of the Johns Hopkins Hospital, but many have been received from the Union Protestant and St. Agnes' Hospitals and elsewhere. During the years 1889 to 1908, almost twenty years, we have accumulated in the laboratory records of 70 cases of cancer of the tongue. In the last five years we observed 30 cases. During the past five years much emphasis has been placed upon the precancerous lesion and the early recognition and treatment of the malignant lesion. The results of this education of the students is shown in the great change in the character of cases of cancer of the tongue. In the first period there were 6, or 23 per cent., of precancerous benign lesions; in the last period, 9 cases, or 33 per cent. In the first period the percentage of inoperable cases was 18, or in the last period this has been reduced to 10 per cent. The cures in cases of undoubted cancer during the first period was but 21 per cent. (5 cured cases). In the last period 6 cases, or 50 per cent., are free from any evidence of recurrence today. The usual time of recurrence after operation for cancer of the tongue is less than nine months, and in all of these cases, recorded as cured, a period of at least nine months had elapsed since operation. This increase in the percentage of cured cases is due, I believe, to the fact that the patients have sought advice earlier; some of the better results may be attributed to better surgery. Here, therefore, we have rather startling figures; precancerous lesions increase from 23 to 33 per cent; very late inoperable cases drop from 18 to 10 per cent; operative cures increase from 21 to 50 per cent.

Cancer of the Breast. During the first period up until 1908 the inoperable cases of cancer of the breast were 27.5 per cent. which has in the past five years fallen to 18 per cent. The percentage of five-year cures up to 1908 was 35 and up to 1913, 42. The difference between early and late intervention is shown by the following figures: In those cases of cancer of the breast in which the diagnosis could not be made clinically, but was made after exploration of the lump, the percentage of five-year cures has varied from 85 to 100. In adenocarcinoma, the least malignant form of carcinoma of the breast, there are 15 cases, all of

which have remained well since operation. In the more malignant types of cancer of the breast subjected to operation in this early period there have been 12 five-year cures, or 85 per cent. We have called this group of cases of cancer of the breast "clinically benign." There has been found at the examination only a palpable lump; there were no changes in the nipple or skin which could be looked upon as signs of malignancy. In gross appearance and under the microscope these clinically benign cases of cancer do not differ from those in the second group called "clinically malignant." The difference between these groups is *clinical only*. In the clinically malignant group the diagnosis of cancer was made from the infiltration of the tumor associated with changes in the nipple and skin. The disease in this group was undoubtedly in a later stage. The difference in the results is startling. In adenocarcinoma the percentage of cures in the benign group is 100; with the same cancer clinically malignant it is but 64. That is, a woman whose lump is an adenocarcinoma, if she delay until the diagnosis of cancer can be made clinically, reduces the probability of her cure from 100 to 64 per cent. In the more malignant types of cancer the probability of a cure is reduced from 85 to 33 per cent.

After a most careful investigation of all the facts available from about 1300 cases of tumors of the breast, we may formulate the following conclusions: If every woman over twenty-five years of age were to seek surgical advice the moment she felt a lump in the breast and the surgeon explored this lump at once, the probabilities are that the lump would prove to be benign in about 33 per cent. of cases; in the malignant cases the chances are that the tumor would be adenocardinoma in 20 per cent. of the cases, with the probability of a cure of 100 per cent. If the lump represented the most malignant forms of cancer, the chances are 85 per cent. of a cure. Now, with the same *good* surgery, these figures should improve as the number of early cases increases. For undoubtedly many cases of cancer subjected to operative treatment late had been distinctly benign lumps for months or even years. The danger of incomplete surgery in the early stage of cancer has been fully discussed in another publication.[2]

Carcinoma of the Lip. In about 200 recorded cases I find that the benign precancerous lesions have increased tremendously, especially in the past two years. Of 12 cases which must be looked upon as distinctly benign and in which two years or more have elapsed since operation, there has not been a single failure to cure. In a group of 16 cases which may be looked upon as early cancer (malignant warts) there has been but one failure to cure, that is, the percentage of cures is about 96. In this case the local lesion,

[2] Jour. Amer. Med. Assoc., September 20, 1913, lxi, 911.

the malignant wart, involved almost the entire lower lip. There was a local recurrence due, I believe, to incomplete excision. The percentage of inoperable cases is also diminishing. When we consider the fully developed carcinoma of the lip in which five years or more have elapsed since operation, we have the following figures:

Group 1. Excision of lesion on lip only 7 cures, or 63 per cent. The failure to cure in 4 cases was due to metastasis to the glands beneath the jaw.

Group 2. Excision of lesion on lip and of the glands beneath jaw. In the cases in which the glands removed showed no evidence of metastasis there have been 20 cures, or 95 per cent. The one failure to cure was due to a local recurrence on the lip (again, probably, incomplete surgery). When the glands removed showed metastasis under the microscope the percentage of cures falls to 50 (6 cases.) These figures, therefore, show that if men will subject themselves to proper surgical treatment for those lesions which precede cancer their chances of a cure should be 100 per cent. Even in the early stage of cancer the proper excision of the local growth on the lip and removal of the glands of the neck should offer almost 100 per cent. Delay, however, with its increasing chances of metastasis to the glands diminishes the probability of a cure.

UNUSUAL TYPE OF ACID INTOXICATION IN INFANTS.

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The term "acid intoxication" has been used somewhat loosely. In infancy and childhood it is produced under varying clinical conditions. It is generally agreed, as was shown by Langstein and Meyer,[1] that acetone in small quantities may occur in the urine of normal children. Acid intoxication results from incomplete fat and protein metabolism, due to functional or organic diseases of the liver or to carbohydrate starvation. It is generally believed that carbohydrate is an important factor in fat and protein metabolism. If the carbohydrate be absent, it is thought that oxidation is imperfect and beta-oxybutyric acid is formed. Beta-oxybutyric acid is not readily demonstrated in the urine, but this acid is further oxidized into diacetic acid and acetone. The presence of acetone is used as a clinical index for the demonstration of acidosis. Mellanby[2] and Sedgwick[3] have shown that

[1] Jahrb. f. Kinderheilk., 1905, lxi, 454.
[2] Lancet, London, 1911, clxxxi, 8.
[3] Amer. Jour. Dis. Child., April, 1912, 209.

creatin and creatinin are excreted in increased amounts during recurrent vomiting attacks. Cathcart[4] found that creatin is constantly present in the urine during starvation, and that carbohydrates given after fasting decrease the creatin, whereas fats given after the starvation increase the creatin. It is, therefore, shown that carbohydrates are required in normal protein metabolism, and also that the elimination of creatin and acetone is produced by similar diets. It is not proved that the production of abnormal acids of the oxybutyric series is without toxic effect. Even though we agree that they are not the primary cause of the condition, nevertheless, they may exert a secondary influence as the result of carbohydrate starvation, whether from persistent vomiting or carbohydrate-poor diet.

A. Loeb[5] recently called attention to the probable toxic effect caused by the administration of acetic acid. He showed that its use may cause acidosis or ketonuria.

It is found that acetone and diacetic acid are present under a variety of clinical conditions. In the infectious diseases acetonuria persists in spite of a considerable carbohydrate ingestion, probably due to some basic alteration in metabolism. Considerable acetone is found in the urine of children who are recovering from chloroform narcosis. Acetone also occurs in some gastro-intestinal disturbances of children not suffering from inanition. The acidosis of "recurrent vomiting" cannot be explained entirely on the basis of starvation. Acid intoxication results after certain forms of poisoning; phosphorus, which produces tissue necrosis in the liver, is capable of causing most marked acetonuria. Similarly, atropin, morphine, lead, and antipyrin may cause acidosis.

In the acute infectious diseases, particularly diphtheria, scarlet fever, measles, and typhoid, in prolonged starvation from any cause; also in diabetes and malignant disease, marked increase in the production of acetone occurs. Else Liefmann[6] has recently published a report on the occurrence of acetone in children suffering from spasmophilia, in which she attempts to show that the elimination of acetone is constantly increased.

The object of this paper is to call attention to a series of cases which have come under my observation during the past several years. They were severe types of acid intoxication, and usually terminated fatally. They occurred mostly in previously healthy infants at about the weaning period. In most instances the infants came from healthy parents. In one family two children had died from this affection. The third child, whose history will be given below, was similarly attacked, but recovered after a severe illness. Dr. Wesley F. Orr, of Idaho,[7] reports five children

[4] Jour. Physiol., 1909, xxxix, 311.
[5] Jahrb. f. Kinderheilk, Band lxxvii, Heft 2.
[6] Bio. Chem. Zeitschr., 1912, xlvii, 118.
[7] Personal Communication.

in the same family who died with symptoms similar to those which we are about to describe. These cases led us to believe that there is a familial type of the disorder.

CHARACTERISTICS OF THE DISEASE. The illness usually occurs in large, robust, previously healthy infants. In some cases the children show a stationary weight curve for several weeks before the onset. If fed at the breast, they show signs of hunger and dissatisfaction with the food because the breast milk is scanty or of poor quality. Some of the infants in this series were artificially fed for weeks or months before the onset of the illness.

The disease is ushered in by gastro-intestinal symptoms, consisting of more or less diarrhea, and nearly always vomiting. The patients are at first restless and show moderate febrile reaction during the first days of the illness, rarely exceeding 101°. Later on the temperature tends to be lower, averaging between 99° and 100°. On the second or third days there is some abdominal distention, dyspnea, with rapid respiration and an increase in pulse-rate. The respirations are labored, and the accessory muscles of respiration show marked activity. The liver is markedly enlarged, the edges are plump, and the surface firm. The urine soon contains albumin, and hyalin and granular casts, without blood, with acetone and diacetic acid. In one of my cases leucin and tyrosin were also found. The urine contains no sugar.

About the third day stupor is noted, which gradually deepens into coma. The blood shows no pathological changes, the leukocytes vary between 9000 and 12,000, and the differential count shows no variation from normal. Toward the close of the disease intestinal atony may occur. As a result, no feces or gas are passed voluntarily, nor can any intestinal evacuation be induced by mechanical or therapeutic agents. Abdominal distention increases progressively, and cyanosis and dyspnea are marked. Unconsciousness continues, and occasionaly vomiting persists until the end. The reflexes are present and normal. There are no symptoms of cranial nerve involvement, and usually no pulmonary complications. When death takes place it usually occurs in four or five days after the onset.

I shall report several typical cases from my clinical records. I have notes on nine cases, not including the severer types of cyclic vomiting, with the presence of large quantities of acetone and diacetic acid. In passing, I may say that a typical case of cyclic vomiting occurring in my practice proved fatal, though such cases are not included in this report.

The first case of this unusual type of acid intoxication came under my observation September 1, 1902.

CASE I.—The patient was one year old; the father was a physician. On August 30, after the infant had been nursed, she was taken seriously ill with vomiting. She vomited several times

during the night: First food, and later on a clear watery fluid. The father administered one grain of calomel in divided doses and other mild laxatives. The child's bowels moved the next day, and she passed gas, though the vomiting continued. On September 2 the following notes were made: Well-nourished female child; slight evidence of rickets; some roughness of the respiratory note over the right upper lobe. Respirations rapid; pulse full, strong, moderately accelerated. Temperature, 99.5° F. Examination of the head, mouth, pharynx, and glandular system of the neck proved negative. The liver was enlarged and felt doughy; abdomen flat; spleen not palpable; no evidence of tumor in the abdominal cavity. There were no meningeal symptoms, though the child was inclined to be stuporous. The following day it was noted that the child was obstinately constipated; the vomiting continued and the abdomen had become slightly tympanitic. The expiratory note in the right upper lobe was an exaggerated vesicular type, though there was no dulness on percussion. On observation it was evident the child suffered from abdominal pain. She was inclined to sleep, though she could be aroused. It is worthy of note that while the temperature was low the pulse was of good quality, though accelerated, and the respirations were extremely rapid, somewhat noisy, and superficial. Later in the evening it was thought that the child passed gas, though there had been no fecal evacuation during the day. She had been given a simple, non-irritating diet. Water was vomited shortly after being given. On the morning of the fifth day the patient developed alarming symptoms, and the father sought the advice of a neighboring physician. The child had not evacuated its bowels for twenty-four hours, and because no gas had been passed, the physician who was summoned concluded that the primary difficulty was a mechanical obstruction of the intestines, and surgical consultation was called. At this consultation the opinion was expressed that the child was suffering from intussusception. This later proved to be incorrect. The following morning the infant's respirations were rapid, pulse feeble, abdomen tympanitic, and the child was plainly in collapse. The urinary examination showed acetone and diacetic acid, a trace of albumin with casts, and an evaporated specimen showed leucin and tyrosin. During the day the child grew progressively worse; stimulation was employed without effect. A careful abdominal and rectal examination gave no evidence of intussusception, nor any other form of mechanical obstruction of the bowel. Crepitant rales were heard over the right upper thorax.

September 4. The child died at 7 P.M.

September 5. Autopsy was performed, with the following findings: The abdomen contained no free fluid; the peritoneum was smooth, shining, and somewhat injected. The great omentum and

the mesenteric glands were normal. A systematic examination of the bowel showed no adhesions or inflammatory reaction in the mesentery or in the serosa covering the bowel; no intestinal obstruction of any kind or nature; mesenteric glands were not enlarged. The spleen was about normal in size, and presented no pathological change. The liver was striking, because it was markedly increased in size, and presented a light yellowish terra-cotta appearance.

The liver on section showed that the surface was glistening, decidedly yellow, and the knife was greasy because of the fatty nature of the tissues.

The capsule of the kidney stripped readily. The cortical markings were obliterated; turbid urine exuded from the pelvis. There was no vascular engorgement, though fatty changes were present.

In the intestine an occasional Peyer's patch stood out prominently, and was the site of an inflammatory reaction.

The lungs showed small areas of focal inflammation and congestion at the bases.

The heart muscle was light in color, though it was well contracted. The valves were normal.

The histological study was made by the late Dr. Howard T. Ricketts. His report is briefly abstracted herewith: A study of the liver showed that the markings of the lobules were not distinct. There was no increase in the connective tissue of the liver. The liver cells stained poorly. Fatty degeneration of the parenchymatous cells was extreme and widespread, being more marked in the periphery of the lobules than in their centres. Little protoplasm was left in such cells, and what remained was granular. The centre of the lobules showed marked granular degeneration. There were also many small areas where neither the nucleus nor the cell body was stained; no normal liver tissue was seen. Many large bacilli not staining by Gram were present, but had no distinctive distribution. In the lungs the vessels were congested. There were certain areas in which the air cells were filled with red-blood corpuscles, though there were a few leukocytes among the extravasated red cells. Moderate fatty degeneration was found here and there in the parenchyma of the kidneys. There were no hemorrhages.

Summarizing the histological findings one notes:

Heart: Moderate focal necrosis.

Lung: Acute hemorrhagic lobular pneumonia (Diplococcus pneumoniæ, probably). Moderate necrosis of epithelial cells. General pulmonary congestion.

Liver: Extensive granular and fatty degeneration, the picture resembling acute phosphorus poisoning.

Kidney: Acute granular and fatty degeneration of the parenchymatous tissue.

In my series of nine cases four autopsies were performed, with findings like those described above, the predominating feature being fatty degeneration of the liver and other organs.

CASE II.—A male child, aged one year, who had been previously weaned and was receiving artificial food, entered the hospital August 1, 1911. He was taken sick three days previously, suffering from moderate diarrhea, having three to five stools daily. The baby vomited several times after nursing. A slight fever was observed during the first day of the disease. He had been restless, cried much of the time, and suffered from abdominal distention. On the third day of the illness he developed a mild stupor. The mother becoming alarmed, sought the hospital. On admission it was noted that the baby was well-developed, well-nourished, and was breathing rapidly and superficially; pulse, 172; respirations, 49; temperature, 101.4° F. Examination of the heart and lungs was negative. The liver was distinctly enlarged; the spleen was not palpable; the abdomen was moderately distended. In a short time the temperature was found to be 99°, pulse 160, and respirations 40. The urine was acid, contained a faint trace of albumin, no sugar, though a marked quantity of acetone and diacetic acid, an occasional leukocyte, but no red cells. The baby died twelve hours after admission to the hospital. No autopsy was permitted.

CASE III.—On October 2, 1911, a physician brought his child to us from a neighboring city. A male child, eleven months old, had made phenomenal gain in weight. At seven months of age he weighed twenty pounds. After the seventh month he remained stationary in weight. For the past three weeks the patient had been unable to satisfy his hunger at the breast. He was nursed every hour to every hour and a half, whereas previously he had been nursed every three hours. The mother noted that her breast milk had been scarce, and that she herself had lost in weight during the past several weeks. Four days before admission to the hospital he was weaned from the breast. He refused all nourishment and took only water. For the next few days he took little or no food. The bowel movements were regular, and he urinated frequently. On October 1, he became constipated, and had no bowel movement; previously he had two or three evacuations a day. October 2, he started to show signs of dyspnea, the respirations became rapid, and later in the day he became stuporous, with a pulse of 140. Constipation persisted, and he continued to refuse all kinds of food except water, which he desired at frequent intervals. He vomited every three or four hours. The examination was for the most part negative; the abdomen was slightly distended; the liver extended three fingers' breadth below the costal arch, and seemed doughy on palpation. The urine contained albumin, hyalin and granular casts, and acetone and diacetic acid in abundance. He succeeded in having several bowel movements on the day of admission, and expelled some flatus. The treatment consisted of the administration of sodium bicarbonate solution by mouth; atropin, grain $\frac{1}{1000}$ by mouth; twenty drops

of brandy, repeated at short intervals; and strained oatmeal gruel was used as food. In addition to the above a solution of sodium bicarbonate was given subcutaneoulsy, and 8 per cent. of glucose in normal salt solution was given by rectum, using the drop method. He died October 3, at 1.45 P.M. No autopsy was permitted.

CASE IV.—H. B. T., male child, aged six months; was born normally; weighed eight pounds; gained steadily in weight; erupted first teeth at four months; had six teeth at six months, and sat erect. Was a large, strong, robust child; had mother's milk exclusively since birth. Was somewhat colicky during the first month of life, and since four weeks of age had been nursed five times in twenty-four hours. No other foods were given; no fruit or vegetable juices. He never had a sick day until the onset of the present illness. Three days before the admission to the hospital he weighed twenty pounds and four ounces, having gained five ounces in the past week. The bowels moved once or twice a day, and the movements were normal. The baby always slept well and showed no urinary symptoms. On the first day of the illness the stool contained mucus, and was of a greenish color, though the infant appeared as well as usual. The next day the infant again had two bright green stools, though he appeared well. The third day the infant had another greenish stool, but since that time (twenty-four hours) had had no bowel movement. Cried at intervals, and seemed restless and uncomfortable. At 6 A.M., September 26, 1912, it was noted that the child began to breathe rapidly and heavily, became languid and drowsy, passed very little urine, and bowels became obstinately constipated. He became cyanosed, had a drawn expression of the face; slight fever, 99° F.; pulse, 120.

The Family History. The father suffered from headache since boyhood; the father's mother had had headaches; the father's father died from alcoholism; a brother was epileptic. The mother stated that her health was perfect in every way: no chronic disease and no tuberculosis. The mother's sister has a goitre. Her parents are living and well. The patient has a sister, five years old, who has always enjoyed good health. Two children in this family died from a condition resembling the present attack of the patient. The first child lived eleven months, was being weaned, and was having a few bottles of cows' milk daily in addition to breast feeding. The baby had been on mixed feedings for three weeks, when he showed signs of indigestion, with greenish stools, though he was not severely ill. After persisting three or four days the patient suddenly was seized with rapid breathing, followed by stupor, and he died in forty-eight hours. The second child, a boy, aged nine months, very large and well-developed; died eighteen months previously; he was fed at the breast, and was given one bottle a day. This feeding had gone on for three or four weeks. At the

expiration of this time he showed signs of indigestion, with greenish, mucous stools, and within a few days began to breathe rapidly, was stuporous, bowels were constipated, and on the fourth day he went into coma, and remained comatose until death, which occurred on the sixth day.

The third baby of this family, the subject of this clinical record, was admitted to the hospital on September 26, 1912; temperature, 101° F.; pulse, 120; respirations, 36. The respirations were rapid and superficial; the infant was cyanosed. The general examination of the head and thorax was negative. The liver was enlarged, though the spleen was not palpable. The reflexes were all somewhat exaggerated. The skin showed a peculiar, pasty appearance. There was no edema. The stools were slightly increased in frequency, greenish and watery, and of a peculiar, penetrating, sour odor. The child was irritable and restless at times, and often fell into a profound sleep. In order that I might study the condition accurately, the mother's urine was collected, and her breast milk was subjected to various examinations. Examination of the *mother's* urine made on the first day of admission to the hospital showed: specific gravity, 1.030; faint trace of albumin; 0.7 per cent. sugar; trace of acetone; no diacetic acid; a few epithelial cells; a few leukocytes; no casts; the fermentation test for sugar was negative. The *infant's* urine, examined about the same time, showed a faint trace of albumin; no sugar; acetone and diacetic acid; ammonia, 0.0952 per cent. Upon testing the baby's urine with the polariscope and by chemical methods no sugar was present. The sugar rapidly disappeared from the mother's urine. A tolerance test for sugar in the mother was made by the ingestion of 140 grams of sugar; urine taken two and four hours afterward showed no sugar by Fehling's test or the polariscope.

For the next few days the infant was extremely ill: showed abdominal distention, vomited occasionally, and had a tendency to be drowsy. On October 1, he became much worse: respirations were increased; pulse small and intermittent; on account of what seemed *a disastrous* collapse, he was given a 2 per cent. solution of sodium bicarbonate subcutaneously in the interscapular region. An examination of the urine at this time showed that it was alkaline, with a marked acetone and diacetic acid reactions. After a precarious night the baby seemed better, next morning, though the area where the subcutaneous injection had been given showed a marked tendency to gangrene and sloughing. The following day the baby presented general edema; puffiness of the face and scrotum; the skin everywhere edematous; no albumin in the urine; and the acetone and diacetic acid were markedly less.

The mother's milk showed 5.5 per cent. of fat; no acetone or diacetic acid. The breast milk was fed to a kitten, and was injected subcutaneoulsy into guinea-pigs and rabbits without in any case

producing the slightest toxic effect. No acetone or diacetic acid was recovered from any of the animals that were tested. After ten days of severe illness the edema disappeared, the patient gradually became playful and happy, and except for the large slough between the scapulæ, was perfectly comfortable.

The treatment consisted of weaning the baby from the breast milk, giving rectal infusions of 8 per cent. glucose in normal salt solution, large doses of sodium bicarbonate by mouth, of whisky, or sour wine in half-dram doses every two hours; powdered casein in half-dram doses in oatmeal-gruel every two hours; soy-bean soup three times a day; occasional oxygen inhalations when cyanosis and dyspnea were most marked; and the subcutaneous infusion of sodium bicarbonate. Two per cent. levulose and sodium bicarbonate were given by mouth. The patient made a complete recovery, and has progressed up to the present time, with an occasional upset. The mother makes almost daily examination of the urine, testing for acetone and diacetic acid, and on one or two occasions has discovered the faintest trace. Aside from this the patient has remained well up to the present time.

The interesting points about this case may be summarized as follows: Previously healthy baby was taken suddenly ill with gastro-intestinal symptoms, diarrhea, and vomiting. Enlargement of the liver followed in a few days by rapid breathing, and a marked quantity of acetone and diacetic acid in the urine. The baby showed irritability and discomfort, and at times a tendency to coma, and finally made a complete recovery.

The most striking feature of this case was the fact that two other infants of this family had previously fallen ill the same way and had died. It is noteworthy, too, that the mother showed some urinary changes upon the admission of the infant into the hospital. Though normally a calm and self-possessed woman, she was suffering from the most intense suppressed emotion because she felt that she was about to lose her third child in the same way that she had previously lost two. Possibly this may explain the glycosuria in her case. At any rate it soon disappeared, and her breast milk, which was examined chemically and injected and fed to animals, as already stated, gave no toxic reaction.

It may be thought that these cases bear a clinical identity with cases of cyclic vomiting; but in this type, vomiting is not so persistent, and sometimes scarcely occurs at all. In my series of cases of unusual acid intoxication the disease described occurs in young infants, often toward the close of lactation.

Persistent and uncontrollable emesis characterizes the cases of cyclic vomiting. Rapid, superficial breathing, enlargement of the liver, low temperature and rapid pulse, with the occurrence of tympany, obstinate constipation, with little or no vomiting toward the end, are features of the type which I am now describing.

A series of cases similar to those which I have enumerated were described by Dr. Thomas D. Parke,[8] of Birmingham, Alabama, before the section on diseases of children at the meeting of the American Medical Association in 1907. Dr. J. Ross Snyder, of the same city, has seen the same class of cases, and has made verbal reports to me. They were mostly in infants who varied from six months to twenty months of age. Most of Parke's cases were breast-fed, though a few were artifically nourished.

In the literature one finds scant mention of this extreme form of acid intoxication in infancy. Possibly some of the severer forms have been described as cases of acute yellow atrophy of the liver, though in none of our cases was jaundice present. The liver remained constantly large, not atrophied, as in cases of acute yellow atrophy. The presence of leucin and tyrosin is not pathognomonic for acute yellow atrophy, since both substances may be found in small amounts in urine in extreme degenerative diseases of the liver, such as afebrile jaundice with slight hepatic enlargement, leukemia, typhoid fever, and other diseases.

From the urinary findings, from the symptom-complex, and from the almost universally fatal termination we are justified in assuming that some profound intoxication has taken place in the infant's organism. The symptoms which this disease group represents have suggested resemblance to the so-called "milk sickness," a condition which has been observed throughout the pioneer portions of the United States where cows became ill with the so-called "trembles," and human beings who partook of milk from such animals or ate of their flesh fell ill with a diseased condition which resembled, in some respects, the cases which we are describing. Human beings ill with this disease show languor, loss of appetite, and extreme constipation, usually marked nausea; the breath has a peculiar, sweetish odor. The pulse is quick, full and soft, and the patients have little or no temperature; drowsiness and coma are not uncommon, and irritability, convulsions, and marked delirium may occur. Notwithstanding the resemblance, those cases which we report, as well as those reported by Parke, were for the most part breast-fed infants by healthy mothers. These cases occurring frequently toward the close of the period of lactation lead us to ask whether there was some quantitative change in the breast milk sufficiently marked to produce the condition of starvation. Thus in the third case mentioned the baby had not gained weight for four months before he came under observation, and for three weeks previous to admission into the hospital he had appeared unable to satisfy his hunger while at the breast. For this reason he had been nursed every hour or hour and a half, whereas previously he had been nursed every three hours.

[8] Jour. Amer. Med. Assoc., 1907, xlix, p. 1827.

Could a starvation acidosis have resulted, or was there some deficiency in the component parts of the breast milk which could have led to a severe intoxication?

Referring to CASE IV, (H. B. T.), the baby was plump and rotund, was receiving large quantities of breast milk, and indeed all of the infants who came under observation were well-developed, usually above the average. One would hardly conceive that these infants were in a condition of starvation, especially if they be compared with the cases of marasmus and decomposition which one so frequently sees as the result of prolonged food deprivation without any evidence of the extreme acid intoxication, or the fatty degeneration of the internal organs which we found in our series of cases. Or is the condition possibly due to a toxicity of the food *per se?* All of the animal experiments which we made showed the milk to be free from poisonous effect. It may be held that this proof is insufficient and that the small animals may have remained free from toxic symptoms, whereas the baby might have succumbed. The milk was injected in considerable quantity in guinea-pigs and rabbits and was fed to kittens. We would have expected some results if toxic products had been present. In addition, some infants, as has been pointed out, were exclusively breast-fed, while others were being artificially nourished. We conclude, therefore, that the cause did not reside in the toxicity of the food before ingestion.

Dr. Parke in his paper suggests the possibility of a bacterial origin because of the usual absence of high fever and the moderate leukocytosis. As one studies these cases he becomes impressed with the fact that the disease seems less likely to be infective or bacterial in origin than a profound metabolic disturbance. Leucin and tyrosin were found in one of our cases marked by extreme fatty degeneration of the liver. The production of these substances may be explained by the destructive cellular changes in the liver, or may be due to a breaking down of the proteids into amino-acids, and of these acids into leucin and tyrosin. In the severer cases of acute yellow atrophy these amino-acids are present in the liver as well as in the blood and in the urine, and hence leucin and tyrosin may be formed outside of the liver in other organs.

The case which recovered under treatment received considerable proteids in the form of casein, gelatin, soy-bean flour, and the animal broths, together with carbohydrates. We assumed that the patient had an intolerance for fat, consequently carbohydrates were given in abundance in the form of cooked starch and levulose. It is possible that the protein of the food was the toxic agent, though in our plan of feeding during the convalescence the protein disturbances seemed to act not unfavorably. Nor do we think that the condition should be considered in the light of an ana-

phylaxis, for many of the infants received the proteid in the form of breast milk. It may be suggested that the carbohydrate intake was insufficient to protect the fat and proteid metabolism, and possibly in this way a perversion of metabolic process occurred, so as to give rise to incomplete or toxic products, with a consequent acidosis and subsequent tissue degeneration.

Recent work has shown that toxic substances can be obtained from every protein that has been subjected to hydrolysis. This includes egg-white casein as well as bacterial proteids. Jobling and Bull[9] have demonstrated that in bacterial proteids, probably in all porteid substances, the toxic products are found in the proteose fraction of the split products (one of the first products of protein cleavage). It has also been shown that under certain conditions the epithelial barrier of the intestines permits the large protein molecule to pass through. This has been demonstrated by the use of egg-albumen, giving rise to an alimentary albuminuria when small doses of protein were administered by mouth.

In seeking to assign a suitable cause for these unusual types of acid intoxication, it has seemed to me—from clinical experience, some experimental work, and therapeutic results—that the disease in question depends upon some derangement of the infantile metabolism, resulting in the production of toxic products from misdirected chemical processes.

The analogy based on the familial occurrence of the disorder in one of our cases leads us to note that an inherent weakness of cells or organs may exist, as in diabetes mellitus, where a marked predisposition to the disease occurs among entire families.

The cases reported by Parke, already referred to, seem identical with those contained in this report.

If I have described a disease group which has been previously classified or reported under another name, the literature has been inaccessible to me, or has not come to my notice. At any rate, the current text-books and periodic literature make no mention of these cases.

EXPERIENCE WITH NEOSALVARSAN AT THE HARLEM HOSPITAL.

By Howard Fox, M.D.,

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Neosalvarsan is now so well known that it is almost useless to burden this report with a description of its various physical

[9] J. Ross Snyder, personal communication.

and chemical properties. I simply wish to give my experience with 175 tubes of this remedy which were kindly given to me last year by Professor Ehrlich for experimental purposes.

The work was done in the out-patient department of the Harlem Hospital, the patients being allowed to go to their homes immediately after treatment. As it had been my custom for a year or more to treat all of my salvarsan cases in an ambulatory manner, I had no hesitancy in following the same plan when using neosalvarsan. The only disadvantage in not keeping the patients in the hospital wards was that they could not be observed quite as closely. It was also impossible to record the temperatures after injections, a matter which did not seem of very vital importance.

FIG. 1.—Ulcerating gumma of one year's duration.

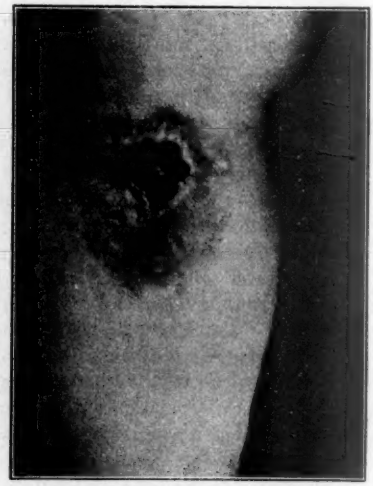

FIG. 2.—Lesion in Fig. 1. Not entirely healed at the end of eight months after four intravenous injections of neosalvarsan.

Of the 56 patients that were treated, 45 were given intravenous injections: 1 of these received two, 17 received three, and 27 received four injections, the treatment being given as far as possible every other day. The intramuscular method was tried in 11 cases, 1 patient receiving two and the others single injections. No other antisyphilitic remedy except neosalvarsan was given.

The cases that were selected for treatment included various forms of cutaneous syphilis, mucous membrane, eye and bone lesions, a few cases of latent syphilis, and one of tabes. Macular eruptions disappeared, as a rule, within a week after treatment. Some of the papular syphilides disappeared in two to four weeks, while in one case (No. 32) the eruption was still apparent at the end of two

months. Several cases of the pustular syphilide, including one of rupial type (No. 46) responded favorably to the new remedy.

In the treatment of several cases of the nodular syphilde the result was as gratifying as that usually obtained from the use of salvarsan. In the treatment of gummas of the skin and mucous membranes the effects of the remedy varied considerably. A deep ulcerative gumma of the leg (No. 11) (Figs. 1 and 2) had not entirely healed at the end of eight months, the patient having received four intravenous injections, although an extensive nodular syphilide upon

FIG. 3.—Ulcerating gumma of one month's duration.

FIG. 4.—Same lesion as Fig. 3, three months after four intravenous injections of neosalvarsan.

another part of the body had healed promptly. A satisfactory result was obtained in a deep gummatous ulcer of the leg (No. 3), the lesion being completely healed in three months (Figs. 3 and 4).

Mucous membrane lesions showed the same tendency to rapid disappearence that is so characteristic of salvarsan. One case of condylomata, however, did not clear up until the end of five weeks, although three intravenous injections had been given. There was no objective change in a case of leukoplakia (No. 17).

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The eye manifestations included one case of iridocyclitis (No. 35), which cleared up in three weeks. In another patient (No. 16) presenting a papular syphilide, an iritis occurred during the course of treatment. This appeared on the day after the second injection and disappeared in about three weeks. A most gratifying result was obtained in a case of marginal keratatis occurring in an adult (No. 49). Twenty-four hours after an intramuscular injection the redness and photophobia had disappeared, and on the third day the patient was able to read. A case of hereditary interstitial keratitis not only failed to improve after three injections, but at the end of one month the second eye became involved. The patient was finally given inunctions of mercury, and showed some improvement at the end of four months. Two cases of optic atrophy (Nos. 24 and 27) and one case with paralysis of the superior rectus muscle and ptosis (No. 43) showed no change as a result of treatment.

A brilliant result was obtained in the following case (No. 21): A man, aged thirty years, suddenly complained of intense hemicrania followed by protrusion of the left eyeball downward and outward. The vision fell to mere perception of light. Examination of the fundus showed nothing abnormal. He had been infected with syphilis ten years previously, and gave a 4 + Wassermann reaction. He was given four intravenous injections, and in ten days the exophthalmos had disappeared and vision in the affected eye had improved to $\frac{20}{30}$. He had not shown any relapse at the end of five months.

The result of treatment in several cases of bone syphilis was most satisfactory. One patient (No. 47) had suffered from osteopereostitis of the tibia for two years, causing her a good many sleepless nights and some difficulty in walking. No relief had been obtained in taking mercury for a year. She was given a single intramuscular injection, after which the pain disappeared almost completely in twenty-four hours, and at the end of a month she could walk without any difficulty. Within six months she had gained fifteen pounds in weight. The improvement was also shown by the *x*-ray photographs, kindly taken by Dr. William H. Stewart, who reports upon them as follows: "'Fig. 5, an anteroposterior view of the left tibia, shows marked productive osteitis, with here and there light shadows indicating the foci of inflammation. The picture is characteristic of the productive bone lesions of syphilis. Fig. 6, taken in approximately the same position, six and one-half months after treatment, shows a considerable change. The condensing process is not nearly as extensive, and shows general absorption. In certain places the medullary canal can be differentiated from the cortex. The areas of rarification are more extensive and cast less dense shadows, indicating further absorp-

tion. In other words, a considerable improvement has taken place."

Another patient with pereostitis of the knee and ankle (No. 37) was given four intravenous injections. Although the knee had been stiff for six months, it became perfectly normal on the day after the second injection. In a case of osteopereostitis of the femur (No. 44) of three years' duration, no improvement resulted from four intravenous injections except a lessening of pain during the night.

FIG. 5.—Osteoperiostitis of tibia. Before treatment.

FIG. 6.—Osteoperiostitis of tibia. Six months after one intramuscular injection of neosalvarsan.

An interesting case of osteoporosis (No. 14) was treated at the request of Dr. William H. Luckett. The patient had previously suffered from four fractures of the right and three of the left femur, and at the time of treatment was recovering from another fracture of the left femur. As the Wassermann reaction was strongly positive

she was given four intravenous injections of neosalvarsan. This resulted in a lessening in the strength of the reaction, although the x-rays showed practically no change in the bone. The condition shown in the radiograms (Figs. 7 and 8) is described by Dr. Stewart as fol-

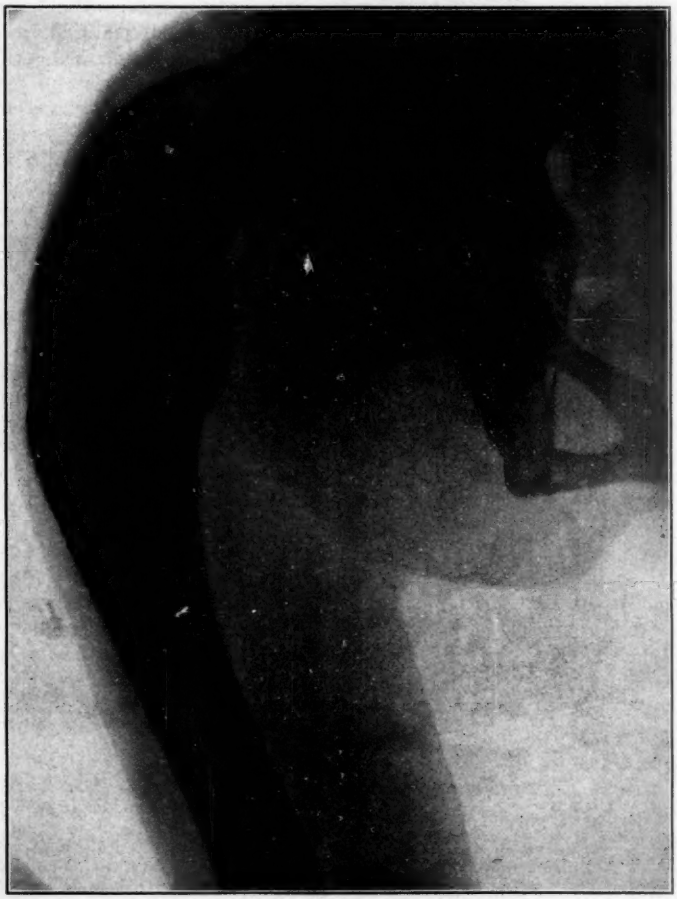

FIG. 7.—Osteoporosis.

lows: "The most typical lesions are seen in the upper third of the femur in and around the acetabulum. These portions are markedly deformed, the convex surface being directed upward, indicating the softening, the deformity being produced by the body weight.

Marked trabeculation and loss of bony substance is noticed in irregular areas. The main outline of the cortex is still retained. The condition seems to me to come under the classification of Bloodgood as cystic degeneration of bone."

FIG. 8.—Osteoporosis.

In two cases of latent syphilis with persistent headaches there was only temporary improvement after treatment. One case of tabes (No. 4) showed an improvement in gait and in general strength, though since the last injection he has been sexually impotent.

In general the symptomatic effect of neosalvarsan was satisfactory. It was analogous to that of salvarsan, though apparently a little weaker. The effect upon the Wassermann reaction was, however, far from satisfactory, and was, in my opinion, considerably weaker than that of a corresponding amount of salvarsan. The Wassermann tests were performed so far as possible at monthly intervals. The technique that was followed was the Thomsen modification, the method employed at the Statens Seruminstitut, at Copenhagen. A definite amount of an alcoholic extract of a normal heart served as antigen, decreasing amounts of patient's serum were used, and the complement titrated.

Of 36 cases treated by three to four intravenous injections, and followed serologically on an average of over five months, 1 case became completely negative and remained so for four months; 2 became negative and 2 almost negative, but later relapsed and became partially positive. A lessening in the strength of the reaction took place in 16 cases, while in 15 cases there was no change.

In giving the intravenous injections it was unfortunately not possible to follow the request of Professor Ehrlich, to use water that was absolutely freshly distilled. A fresh supply was only obtained at intervals of two weeks. It was possibly due to this reason that in my series of 161 intravenous injections the following symptoms were noted. Chills or chilly sensations were reported after twenty-seven injections, nausea after thirty, vomiting after ten, diarrhea after three, headache after four, dizziness after six, malaise after five, and abdominal cramps after three injections. Many of these symptoms were extremely mild, and did not prevent the patients from returning for further injections, which were given with fairly great regularity, as can be seen by a glance at the accompanying tables. In a single case (No. 38) the patient felt sick enough to be taken into the hospital for three days. He complained of severe nausea, general pains, and presented an edema of the face. The temperature, however, did not rise above 100°.

Among the general effects of the treatment with neosalvarsan should be mentioned an improvement in appetite, which occurred in a great majority of cases. A gain in weight was also frequently observed, 11 patients gaining an average of thirteen pounds while 1 woman gained twenty-six pounds in six months.

There was no disturbance in the menstrual function in any case.

The Herxheimer reaction was particularly marked in 2 cases (Nos. 32 and 36), being noted by the patients themselves. In another case (No. 31) an erythematous rash appeared upon the face, arms, and legs four days after injection lasting two days,

and being accompanied by a temperature of 100° and slight malaise.

The local effects of the intravenous injections were much less disturbing to the veins than injections of salvarsan. They varied from the formation of a tiny nodule to complete occlusion of the vein. The disturbance was so slight, as a rule, that four injections could frequently be given in the same vein within a period of nine days, which would seldom be possible in the case of salvarsan.

The technique of preparing the new remedy with water at room temperature, dispensing with the alkali, etc., is too well known to be discussed in this report. It is sufficient to say that in no case was the vein exposed by cutting down upon it. This procedure, in my opinion, should be avoided whenever possible, as it not only leaves a compromising scar, but destroys any further usefulness of the vein for injection or blood-letting purposes. By inserting the needle directly through the skin much time is also saved. In this way it was possible to give five injections in an hour, with a skilled nurse as an assistant.

The intramuscular method was tried in 11 cases, the remedy being given as an emulsion with iodopin oil. It must be admitted that the results in some of these cases were exceedingly good, and compared favorably with those obtained by repeated intravenous injections. They were, however, decidedly painful in all except two of the cases. The pain, induration, and lameness that followed more than counterbalanced the time and trouble of giving several injections by the intravenous method. Though the experience quoted in this report is limited, I think it is fair to draw the following conclusions:

CONCLUSIONS. 1. Neosalvarsan is an excellent symptomatic remedy for the treatment of syphilis.

2. Its symptomatic action seems to be slightly weaker than salvarsan when used in corresponding amounts.

3. Its serological action seems to be considerably weaker than salvarsan when used in corresponding amounts.

4. It possesses a decided advantage over salvarsan in the greater ease and rapidity with which it can be prepared and injected intravenously.

5. Intravenous injections of neosalvarsan are much less disturbing to the veins than intravenous injections of salvarsan.

For the greater part of the material in this report I am indebted to Drs. Edward Pisko, Benjamin F. Ochs, and Wilmot B. Allen, to whom I wish to express my thanks.

TABLE I.—Cases of Syphilis Treated with Intravenous Injections of Neosalvarsan.

No.	Sex.	Age.	Stage of disease.	Duration of lesions.	Previous treatment.	Neosalvarsan injections.	Clinical results.	Wassermann reaction.
1	F.	40	Papular syphilide	6 weeks	None	Gm. 0.5, June 12 Gm. 0.5, June 14 Gm. 0.5, June 17 Gm. 0.5, June 19	Eruption disappeared 3 days after last injection.	Changed from 4 + to 3 + at end of 6 months. 4 + at end of 9 months.
2	F.	27	Papular syphilide	6 weeks	Hg. internally 10 days	Gm. 0.4, June 14 Gm. 0.4, June 17 Gm. 0.4, June 19 Gm. 0.4, June 21	Eruption disappeared 2 weeks after last injection.	Remained 4 + at end of 9 months.
3	M.	60	Gumma of leg	1 month	None	Gm. 0.6, June 14 Gm. 0.6, June 17 Gm. 0.6, June 19 Gm. 0.6, June 24	Gumma healed in 3 months.	Changed from 4 + to 2 + at end of 5 months. 4 + at end of 9 months.
4	M.	53	Tabes	Infection 20 years previously	None	Gm. 0.6, June 19 Gm. 0.6, June 21 Gm. 0.6, June 23 Gm. 0.6, June 29	Improvement in gait and general strength. Impotent since treatment.	Changed from 3 + to negative at end of 3 months. 3 + at end of 9 months.
5	F.	19	Papular syphilide	3 weeks	None	Gm. 0.3, July 1 Gm. 0.3, July 3 Gm. 0.3, July 5 Gm. 0.3, July 8	Eruption disappeared 2 weeks after last injection.	Changed from 4 + to negative at end of 2 months. 2 + at end of 8 months.
6	M.	20	Papulopustular syphilide	2 weeks	None	Gm. 0.4, July 1 Gm. 0.4, July 3 Gm. 0.4, July 5 Gm. 0.4, July 8	Pustules dried after 3d injection. Crusts fell 2d day after 4th injection.	Changed from 4 + to 3 + at end of 2 months. Remained same at end of 7½ months.
7	M.	28	Gumma of the uvula	1 month	None	Gm. 0.4, July 1 Gm. 0.4, July 3 Gm. 0.4, July 5 Gm. 0.4, July 8	Gumma healed 24 hours after 3d injection.	Changed from 4 + to 3 + at end of 2 months. Remained same at end of 7½ months.
8	M.	30	Maculopapular syphilide	2 weeks	None	Gm. 0.3, July 15 Gm. 0.4, July 17 Gm. 0.5, July 22 Gm. 0.5, July 24	Failed to return to clinic. Later went to Central Islip Hospital where he is said to have shown symptoms of cerebral syphilis.	Wassermann performed at Islip said to have been negative.
9	F.	24	Papular syphilide	3 weeks	None	Gm. 0.3, July 15 Gm. 0.4, July 17 Gm. 0.5, July 24 Gm. 0.6, July 26	Eruption disappeared 1 month after last injection. Patient gained 26 pounds.	Changed from 4 + to 1 + at end of 3½ months. Remained same at end of 7½ months.
10	M.	33	Superficial ulcers of tongue. Pains in tibiæ	3 years Disappearing and recurring	Hg. irregularly in small doses	Gm. 0.3, July 15 Gm. 0.4, July 17 Gm. 0.5, July 22	Ulcers healed 24 hours after 2d injection. Pains in tibiæ disappeared same time. No recurrence at end of 8 months.	Changed from 3 + to 2 + at end of 7½ months.

11	F.	40	Nodular syphilide of neck. Gumma of leg	Nodular syphilide 15 months. Gumma 1 year	None	Gm. 0.3, July 17 Gm. 0.4, July 22 Gm. 0.5, July 24 Gm. 0.6, July 29	Lesion upon neck healed 3 days after 3d injection. Gumma of leg not entirely healed at end of 8 months.	Changed from 4 + to 3 + at end of 2 months. 2 + at end of 8 months.
12	M.	39	Nodulosquamous syphilide of arms, shoulders, and back	9 years	None	Gm. 0.3, July 26 Gm. 0.4, Aug. 2 Gm. 0.5, Aug. 6 Gm. 0.6, Aug. 8	Eruption disappeared 4 days after last injection.	
13	M.	23	Pustular syphilide	2 months	Hg. internally 4 months	Gm. 0.3, July 29 Gm. 0.4, July 30 Gm. 0.5, Aug. 2 Gm. 0.6, Aug. 5	Eruption nearly gone at time of last injection. Failed to return to clinic.	
14	F.	39	Osteoporosis. Fracture of femur	.....	None	Gm. 0.3, Sept. 7 Gm. 0.4, Sept. 9 Gm. 0.5, Sept. 11 Gm. 0.6, Sept. 13	Gained 17 pounds in 7 months. (See text.)	Changed from 4 + to 2 + at end of 6 weeks. 2 + at end of 7 months.
15	F.	30	Gumma of leg	1 month	No Hg.; 1 intravenous salvarsan 1 year previously	Gm. 0.3, Sept. 11 Gm. 0.4, Sept. 13 Gm. 0.5, Sept. 16	Failed to return to clinic.	
16	F..	27	Annular papular syphilide	3 months	None	Gm. 0.3, Sept. 16 Gm. 0.4, Sept. 18 Gm. 0.5, Sept. 20 Gm. 0.6, Sept. 22	Eruption disappeared 1 month. (See text for eye complications.)	Remained 4 + at end of 6 months.
17	M.	49	Nodular syphilide of penis; leukoplakia; ulcers of mouth	Nodular syphilide and ulcers 6 weeks	Hg. internally for 6 months	Gm. 0.3, Sept. 23 Gm. 0.4, Sept. 25 Gm. 0.5, Sept. 27 Gm. 0.6, Sept. 30	Nodular lesions disappeared in 1 week, and ulcer 2 days after last injection. No objective change in leukoplakia.	4 + at end of 5½ months.
18	M.	40	Maculopapular syphilide	4 months	Hg. internally for 1 month	Gm. 0.3, Sept. 23 Gm. 0.4, Sept. 25 Gm. 0.5, Sept. 27 Gm. 0.6, Sept. 30	Eruption disappeared 10 days after last injection.	Changed from 4 + to 3 + at end of 8 weeks. 2 + at end of 5½ months.
19	M.	44	Macular syphilide	1 month	None	Gm. 0.3, Sept. 27 Gm. 0.4, Sept. 30 Gm. 0.5, Oct. 2 Gm. 0.6, Oct. 4	Eruption disappeared 6 days after last injection. Failed to return to clinic.	
20	M.	22	Gumma of fauces	1 month	Hg. internally for 2 weeks	Gm. 0.3, Oct. 4 Gm. 0.4, Oct. 6 Gm. 0.5, Oct. 16	Gumma healed 3 days after 2d injection.	4 + at end of 6 weeks.
21	M.	30	Exophthalmos	2 weeks	None	Gm. 0.3, Oct. 9 Gm. 0.4, Oct. 11 Gm. 0.5, Oct. 14 Gm. 0.6, Oct. 16	Exophthalmos disappeared in 2 weeks. (See text.)	4 + at end of 3 months. 3 + at end of 5 months.
22	F.	26	Pustular syphilide	1 month	None	Gm. 0.3, Oct. 14 Gm. 0.4, Oct. 16 Gm. 0.5, Oct. 18	Pustules dried 1 week after first injection.	Changed from 4 + to 2 + at end of 4 months. 4 + at end of 5½ months.
23	M.	26	Latent syphilis Persistent headaches	.....	1 injection of salvarsan 2 years previously	Gm. 0.4, Oct. 14 Gm. 0.5, Oct. 16 Gm. 0.6, Oct. 18	Headaches disappeared for 2 months and then returned.	Remained + at end of 3 months.

No.	Sex.	Age.	Stage of disease.	Duration of lesions.	Previous treatment.	Neosalvarsan injections.	Clinical results.	Wassermann reaction.
24	F.	32	Chorioretinitis. Optic atrophy	Vision began to fail 5 months previously	5 Hg. injections	Gm. 0.4, Oct. 14 Gm. 0.5, Oct. 16 Gm. 0.6, Oct. 18	No improvement.	Remained 2 + at end of 7 weeks. 1 + at end of 6 months.
25	M.	17	Latent	6 months after infection	None	Gm. 0.3, Oct. 16 Gm. 0.4, Oct. 21 Gm. 0.5, Oct. 23	.....	3 + at end of 7 weeks. Same at end of 6 months.
26	F.	20	Latent syphilis Severe headaches	Headaches 18 months	None	Gm. 0.4, Oct. 18 Gm. 0.5, Oct. 21 Gm. 0.6, Oct. 23	Slight improvement.	Changed from 4 + to 1 + at end of 5 weeks.
27	M.	49	Optic atrophy	1 year	None	Gm. 0.4, Oct. 21 Gm. 0.5, Oct. 25 Gm. 0.6, Oct. 28	No change.	Changed from 4 + to 3 + at end of 5 weeks. 2 + at end of 5 months.
28	F.	14	Hereditary syphilis Interstitial keratitis	1 month	None	Gm. 0.4, Oct. 21 Gm. 0.5, Oct. 23 Gm. 0.6, Oct. 28	Slight improvement at end of 1 month, when other eye became involved. Both eyes improved at end of 4 months.	Remained 4 + at end of 5 months.
29	F.	27	Mucous patches of vulva	2 months	None	Gm. 0.4, Oct. 21 Gm. 0.5, Oct. 23 Gm. 0.6, Oct. 25	Lesions disappeared 2 days after 2d injection.	Changed from 4 + to 3 + at end of 5 weeks. Remained same at end of 5 months.
30	M.	28	Latent syphilis	3 years after infection	Hg. internally for 2 years irregularly	Gm. 0.4, Oct. 28 Gm. 0.5, Oct. 30 Gm. 0.6, Nov. 1	.....	Remained 3 + at end of 5½ months.
31	F.	24	Maculopapular syphilide; condylomata	2 months	None	Gm. 0.4, Nov. 4 Gm. 0.5, Nov. 6 Gm. 0.6, Nov. 8	Eruption disappeared 2½ weeks after last injection. Condylomas disappeared in 5 weeks.	Changed from 4 + to 1 + at end of 8 weeks. Remained 1 + at end of 4½ months.
32	F.	33	Maculopapular syphilide; iritis	3 weeks	None	Gm. 0.4, Nov. 4 Gm. 0.5, Nov. 6 Gm. 0.6, Nov. 8	Iritis cleared up in 3 weeks. Eruption still present, though fading, at end of 2 months.	4 + at end of 9 weeks.
33	M.	22	Annular papular syphilide	5 weeks	None	Gm. 0.4, Nov. 6 Gm. 0.5, Nov. 8 Gm. 0.5, Nov. 11 Gm. 0.6, Nov. 13	Lesions flattened completely in 24 hours after 2d injection. Pigmentation remaining.	
34	M.	21	Mucous patches; pigmentary syphilide	4 months	Hg. internally for 1 week	Gm. 0.4, Nov. 11 Gm. 0.5, Nov. 13 Gm. 0.6, Nov. 15	Mucous patches healed 48 hours after 1st injection. Pigmentary syphilide partially disappeared at end 4 months.	Changed from 3 + to 2 + at end of 5 weeks. 1 + at end of 2 months. Negative at end of 4 months.

35	F.	21	Iridocyclitis	2 months	None	Gm. 0.5, Nov. 18 Gm. 0.6, Nov. 20 Gm. 0.6, Nov. 27 Gm. 0.6, Nov. 29	Iridocyclitis cleared up in 3 weeks.	Remained 3 + at end of 2 months.
36	F.	30	Macular syphilide	4 weeks	Hg. internally for 2 weeks	Gm. 0.4, Nov. 18 Gm. 0.5, Nov. 20 Gm. 0.6, Nov. 25 Gm. 0.6, Nov. 27	Eruption disappeared 1 week after 2d injection; 2 months later sparse eruption of lenticular papules.	Remained 4 + at end of 4 months.
37	M.	26	Osteoperiosteitis of knee and ankle	6 months	Hg. internally for 2 months	Gm. 0.3, Nov. 27 Gm. 0.4, Nov. 29 Gm. 0.5, Dec. 2 Gm. 0.6, Dec. 6	Knee, which had been stiff and painful for 6 months, became practically normal after 2d injection. (See text.)	
38	M.	25	Periosteal gumma	6 weeks	Hg. internally for 6 months	Gm. 0.3, Nov. 27 Gm. 0.5, Nov. 29 Gm. 0.6, Dec. 2	Gumma disappeared 10 days after last injection.	Remained 4 + at end of 4 months.
39	M.	22	Gumma of tongue	1 month	Hg. internally for 3 years	Gm. 0.5, Nov. 27 Gm. 0.5, Dec. 2 Gm. 0.6, Dec. 4 Gm. 0.6, Dec. 6	Gumma completely healed 7 weeks after last injection.	Changed from 4 + to 3 + at end of 10 weeks.
40	M.	43	Nodular syphilide of scalp. Gumma of arm	Nodular syphilide for 3 months; gumma, 1 month	Hg. internally and by inunctions small amounts	Gm. 0.3, Dec. 4 Gm. 0.4, Dec. 6 Gm. 0.5, Dec. 9 Gm. 0.6, Dec. 11	Lesions healed 3 weeks after last injection.	Remained 4 + at end of 3 months.
41	F.	25	Mucous patches of vulva and mouth	2 weeks	None	Gm. 0.3, Dec. 4 Gm. 0.4, Dec. 6 Gm. 0.5, Dec. 9	Lesions healed at time of 3d injection; failed to return to clinic.	
42	M.	26	Ulcerating nodular syphilide	.....	None	Gm. 0.3, Dec. 13 Gm. 0.4, Dec. 16 Gm. 0.5, Dec. 18 Gm. 0.6, Dec. 20	Failed to return to clinic.	
43	F.	52	Paralysis of superior rectus; ptosis	6 months	Hg. internally for 5 months	Gm. 0.4, Dec. 18 Gm. 0.5, Dec. 20	No improvement.	Remained 4 + at end of 3 months.
44	M.	59	Osteoperiosteitis	3 years	Hg. internally for 3 years irregularly	Gm. 0.3, Dec. 30 Gm. 0.4, Jan. 3 Gm. 0.5, Jan. 6 Gm. 0.6, Jan. 8	Pain lessened; no change in size of leg. (See text.s	Remained 2 + at end of 10 weeks.
45	M.	40	Gumma of back	3 weeks	None	Gm. 0.5, Jan. 6 Gm. 0.5, Jan. 8 Gm. 0.5, Jan. 10 Gm. 0.5, Jan. 13	Lesions healed 4 weeks after last injection.	Remained 4 + at end of 3 months.

TABLE II.—Cases of Syphilis Treated with Intramuscular Injections of Neosalvarsan.

No.	Sex.	Age.	Stage of disease.	Duration of lesions.	Previous treatment.	Neosalvarsan injections.	Clinical results.	Wassermann reaction.
46	F.	42	Pustular (rupial) syphilide	6 weeks	Hg. internally for 6 weeks	Gm. 0.4, June 12 Gm. 0.4, June 25	Lesions healed in 9 weeks.	2 + at end of 3 months. Remained same at end of 9 months.
47	F.	38	Osteoperiosteitis of tibia	2 years	Hg. internally for 1 year	Gm. 0.6, Sept. 21	Pain disappeared at end of 24 hours.	Remained 3 + at end of 6 months.
48	F.	37	Latent syphilis; carcinoma of uterus	.....	None	Gm. 0.3, Nov. 6		
49	F.	38	Marginal keratitis	1 week	None	Gm. 0.6, Nov. 8	Redness and photophobia disappeared on 2d day. (See text.)	Changed from 4 + to 2 + at end of 8 weeks. Remained same at end of 4½ months.
50	F.	28	Moist papules	2 months	None	Gm. 0.6, Dec. 2	Lesions healed in 3 days.	
51	F.	24	Gummas of legs and eyelid	On legs 1 month; on eyelid 3 months	Hg. internally for 9 months	Gm. 0.6, Dec. 2	Ulcers of legs partially healed end 3 months; gumma of eyelid well in 1 month.	3 + at end of 5 weeks.
52	F.	38	Gumma of nasal septum	1 month	None	Gm. 0.6, Dec. 2	Gumma nearly healed 4 days after last injection.	
53	F.	49	Periosteal gumma of forehead	5 months	None	Gm. 0.6, Dec. 9	Left clinic and was treated at Mt. Sinai Hospital by 7 injections of neosalvarsan; gumma not completely healed at end of 3 months.	
54	F.	36	Exophthalmos; severe headaches	3 months	None	Gm. 0.6, Dec. 9	Failed to return to clinic.	
55	F.	24	Ulceration of cervix	10 days	2Hg. injections	Gm. 0.6, Dec. 30	Ulceration healed in 2 weeks.	Remained 4 + at end of 10 weeks.
56	F.	38	Ulcerating gumma of leg	18 months	Hg. internally for 18 months	Gm. 0.6, Jan. 3	Ulcers healed at end of 1 month.	Remained 4 + at end of 10 weeks.

THE METABOLISM, PREVENTION, AND SUCCESSFUL TREATMENT OF RHEUMATOID ARTHRITIS: SECOND CONTRIBUTION.[1]

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(Continued from December, 1913.)

Case VII.—Mrs. E., aged forty-seven years, white. Referred by Dr. James E. Talley. This case was of great interest, and was made the subject of a metabolic study. The patient had led an active, useful life in a country village, and considered herself healthy. She had had no children and no miscarriages. Six years previous to admission her ovaries had been removed at the German Hospital, Philadelphia, for pelvic trouble, but she apparently made an uneventful recovery. Shortly after this, however, she experienced at times, in several fingers, a blanching and numbness which were aggravated or precipitated by cold weather. Immersion in hot water restored normal sensation, and, as this appeared, the color changed from white to red and finally purple before the normal hue returned.[1] After persisting a year or so the condition cleared up, except for a very rare and slight suggestion of it in very cold weather.

For a few years past she had been subject to some "sore throat" during the winter months, and had been troubled with belching and headache. Her bowels had always been costive. In the latter part of June, 1912, her left knee became swollen and stiff, followed in two weeks by the right. Since then her ankles, wrists, hands, shoulders, and hips had become involved, until on September 11, on admission to the Presbyterian Hospital, Philadelphia, she could walk only with assistance, and said that for six weeks previously she had been forced to sit all of the time without much changing her position. Appetite was good, but sleep was much disturbed by pain. Examination showed good development and nutrition, with a freely movable right kidney. The wrists, fingers, knees, and ankles were all swollen and somewhat tender upon motion, but, presented no other marked deformity. Examination of the ears and nasopharynx, by Dr. Ben. C. Gile, revealed no focus of infection. The teeth were well cared for. The urine was essentially normal, and was free from indican. Blood examination showed: Red-blood cells, 3,640,000; white-blood cells, 10,400; hemoglobin, 59 per cent. *X*-ray examination of the abdomen showed marked dilatation

[1] Dr. C. B. Farr kindly furnished me with this information from observations made when the patient was under his care. He regarded the condition as suggestive of Raynaud's disease, which has been mentioned by some writers as occasionally prodromal to rheumatoid arthritis.

and ptosis of both stomach and colon, with great elongation and tortuosity of the bowel. The hands and other joints showed both hypertrophic and atrophic changes. Under large doses of salicylates her symptoms improved, and she was advised to leave the hospital, take Fowler's solution, and report for frequent observation until her anemia had improved sufficiently to warrant treatment along the lines to be mentioned presently.

Experience with Case II had seemed to indicate this course, but subsequent study showed it to have been needless. She was treated with arsenic, tonics, ample feeding, and good hygiene, however, from October 23 to December 15, with improvement in her general health and anemia, and subjective improvement in her joints, though swelling and stiffness and pain still persisted.

December 15 she was readmitted to the hospital. At this time she had daily fever up to about 100° or more, a blood pressure of 124 and 60, and weighed 121¼ pounds. For three weeks previously, through a misunderstanding in regard to getting a private room, she had had no arsenic, and was consequently in much pain and discomfort, having pain at night, and being greatly limited in all her movements.

This was deemed a good case in which to study the metabolism, and she was accordingly placed upon the following diet, with the idea of making the observations while she was in an active stage of the disease for the purpose of contrasting them with others made in convalescence.

December 27. She ingested in twenty-four hours the following, divided into three meals: Sugar, 12 grams; butter, 30 grams; toast, 55 grams; egg, 100 grams; rice, 210 grams; milk, 690 c.c.; salt, 1½ grams. This approximated 1375 calories, which with her weight, about 119 pounds gave 11.5 calories per pound of body weight or 25.30 calories per kilo. She had been placed previously for several days upon an unrestricted diet of the above ingredients, with the idea of determining how much of this food she needed and would take during the "metabolic" period. The above figures were therefore of her own choosing. The metabolic figures follow later in the text and are there discussed.

January 1, 1913. Upon the completion of these observations she was placed under the following regimen:

Colonic lavage once a day in the morning; 7 glasses of whole milk daily; 1 slice of toast and butter at breakfast; 1 apple at breakfast; 1 green vegetable at lunch (either spinach, lettuce, celery, turnips, cabbage, or tomatoes), provided it be not cooked with sugar or flour; 1 slice of toast and butter at supper; 1 helping of stewed fruit at supper. This yielded about 1434 calories, slightly more than the first diet, but the calories were differently distributed. In the first period, of the 1375 calories about 200 had come from proteid, about 620 from fat, and about 540 from carbo-

hydrates. In the second diet of about 1434 calories, about 220 had come from proteid, about 753 from fat, and about 461 from carbohydrates. These figures show that the carbohydrates gave fewer and the fats gave more of the total calories in the second than in the first period. This will be referred to later.

The notes made at the time as to her condition here follow under their respective dates:

December 19, 1912. Patient was getting worse steadily; hands were enlarged and knees were painful. Slept fairly well. Appetite was good. Was getting house diet. Had been without arsenic for nearly a month, owing to difficulty of getting a room. For ten days after the drug was stopped she still felt its benefit.

December 28. Metabolic diet began December 24. Bowels well moved at that time, but only slightly since by salt solution or enema. This date distilled water instead of salt solution was used. Had been increasingly poorly since admission until this date. At 5 P.M. said she felt better than she had for two weeks, and could arise from her chair and move her fingers well. Seemed to be losing weight; tongue clean; expression bright.

December 29. Said she felt "pretty good." Not quite so free from stiffness, etc., as the day before, but the difference was not great, and she ascribed it to the constipation. Slept well the previous night. Last three nights had been good. No stool as yet; nothing but scybalous masses the size of a peanut. Tongue clean.

December 30. Knees were slightly stiff to-day, and shoulders also, more so than on previous day. Could move fingers more than five days before. They could be shut passively almost entirely, and there was less swelling. A ring which was tight on admission could be moved to the knuckle freely, and moved around finger. Had less soreness at the left trochanter than prior to December 27. Bowels moved well after enema yesterday at 3 P.M. Patient said she felt a good deal better than one week before; generally, as well as in joints.

December 31. Was slightly worse. Weight now constant at 118½ pounds. Had more pain at night and fingers were more swollen, the right hand being worse than the left. Temperature was apparently working down slightly.

January 1, 1913. Therapeutic diet started.

January 3. Had been on the therapeutic modified diet, seven glasses of milk, etc., since January 1. Slightly better yesterday and slightly improved this date also. Hands not swollen, though all the joints were stiff on waking.

January 4. Unquestionably better. Had a good night, with no severe pain, and slept well. Walked better. Hands were not swollen and fingers hurt only on marked flexion, active or passive. Temperature was lower than for any extended period yet.

January 6. Right knee and right ankle were not quite so well as the day before. Everywhere else she was better. Hands were smaller; could be bent farther and with less stiffness and pain; motions were distinctly quicker than before. Could move both shoulders better, and had a good night. Temperature was barely above 99°. Weight was the same.

January 8. Could not use hands quite so well, though she could hold her hands closed when they were shut. Had slightly more stiffness in the shoulders, as tested by putting her arm over the back of a chair when sitting. Had slightly more pain in her knees, though she could arise fairly well. Temperature seemed to be working lower; hands looked distinctly smaller; the metacarpals showed plainly. Said she felt pretty well, and that bad weather always made her feel worse. Said she would willingly continue on her present diet, even, to retain the improvement to date, such as it was.

January 11. Hands closed better than at any time. Knees were slightly stiffer. Left shoulder pained slightly during the night, but could be moved freely and without pain. No fever. Weight constant. Could pick up heavy books with her hands. Not too hungry, but enjoyed her food. Left hand could be shut passively, and forcibly held without pain.

January 29. Slight "lameness" in both shoulders, especially the left. Motion not so free as previously at one time. "Hands are fine." Insists that she had not felt so well for a long time. Temperature was normal.

February 6. Had stiffness and pain at the angle of the jaws on both sides since onset of disease. Had noticed in this respect an improvement for three to four days previously; this date it was distinctly marked.

February 8. Walked five squares the previous day. Knees were no worse. Shoulder was better. Middle finger of right hand was swollen and sore; began the day before at 4 P.M. Better than during the night. Used finger with a thimble and pressed quite hard while sewing.

February 9. Walked seven squares the day before. Finger was much better. Shoulder also was much better than for two weeks past. Knees were pretty fair.

March 9. Walked the previous day better than at any time yet. Climbed three flights of stairs in the afternoon. Feet and ankles hurt slightly during the night.

March 12. Had been taking an egg at each meal, beginning the day before at lunch. No rise of temperature, and felt well. Slept well at night. Very supple. Was given more cream in coffee today.

March 15. Going home. Bad, rainy day, but felt very well.

At the time of leaving the hospital her weight was 117. Her dietary was as follows:

6.30 A.M.: Milk, 200 c.c.

Breakfast: 1 apple, 150 grams; weak coffee, 120 c.c., with f℥iv of 20 per cent. cream and f℥i of sugar; 1 soft-cooked egg; toast, 16 grams (one-half slice); butter, 13 grams.

10.30 A.M.: Milk, 200 c.c.

Dinner: Bouillon, 120 c.c.; 4 tablespoonfuls of stewed tomatoes; 1 soft-cooked egg; toast, 15 grams; butter, 13 grams; lettuce with 1 tablespoonful of mayonnaise dressing; milk, 1 glass, 200 c.c.

3.30 P.M.: Milk, 200 c.c.

Supper: 1 soft-cooked egg; toast, 15 grams; butter, 13 grams; baked apple, 158 grams; 3 stalks of celery; milk, 1 glass, 200 c.c.

Upon reaching her home the colonic lavage was given every other day for a week and then discontinued entirely. Little by little substitutions and additions were made to her dietary, bearing in mind the caloric values of the foods given, and an effort was made to increase her weight with additions of cream to her milk.

This was successful, so that by May 15, she was able to do a large part of her housework, and weighed 122½ pounds, notwithstanding her greatly increased activities and responsibilities.

She was emphatic in stating that her general health was better than it had been before she was taken ill, that she was free from the gastric distress and headache, which had been frequently present, and that her only complaint was slight stiffness in the evening after reading for an hour or so in one position. Her sleep was excellent, unbroken by any pain, and her spirits were bright.

May 24. Her dietary averaged as follows:

Breakfast: 1 apple; 1 slice of toast and butter; 1 soft-boiled egg; 1 cup of hot water with 1 teaspoonful of cream and 1 teaspoonful of sugar.

10.30 A.M.: 1 glass of milk, with 1 tablespoonful of cream.

Dinner: 1 slice of toast and butter; 1 piece of chicken; 1 tablespoonful of beets; 2 tablespoonful of peas; 1 glass of milk and 1 tablespoonful of cream.

3.30 P.M.: 1 glass of milk, with 1 tablespoonful of cream.

Supper: 1 slice of toast and butter; 1 scrambled egg; lettuce, with French dressing; 2 tablespoonfuls of stewed rhubarb; 1 glass of milk, with 1 tablespoonful of cream.

8.30 P.M.: 1 glass of milk, with 1 tablespoonful cream.

The patient had been constant and careful in adherence to her regimen. She wanted no more than she was taking, and craved no other food, though her appetite was good. June 2, 1913, she weighed 125¼ pounds, 4 pounds more than on admission to the hospital, when she had been taking arsenic, tonics, and forced feeding, and over 8 pounds more than she weighed at one time during the early stages of her therapeutic diet.

About June 27, in the midst of a protracted spell of hot weather, this patient had a regrettable but interesting relapse. She did not appear for treatment until the relapse had lasted ten days, though she had made some reductions of her diet of her own accord. When seen her fingers and wrists were swollen and she complained of her hips. Her diet was further reduced and she was put at rest. On July 1 she was distinctly better, though still not well. In November, 1913, her joints were in fairly good condition and she was adhering to the principles of her diet, but the symptoms of Reynaud's disease had become more constant and considerably more advanced.

This and certain other observations of a similar nature seemed to indicate that during hot weather, when the bodily caloric need is much reduced, the particular caloric intake which has been well tolerated or has been a necessity may become a surfeit, with the result just described. During protracted heat the caloric necessity and tolerance probably decrease, and in the presence of an unstable metabolic equilibrium the adjustment might easily be overthrown.

It should be noticed that this patient had been living presumably near her high limit of food tolerance before this relapse, as she had gained markedly in weight and had been eating relatively freely. An additional complicating factor in this case is the vasomotor instability, as evidenced by her previous attacks suggesting Raynaud's disease. For several weeks before the relapse above described she had had curious areas of local erythema on the palms of her hands or fingers, accompanied often by great itching. The full significance of this accompanying complication cannot be known, but there is little doubt that it aggravated her condition.

Case VIII.—B. de H., female, white, aged thirty-two years. Referred by Dr. William Drayton, Jr., from the dispensary service of the Orthopædic Hospital. As the patient had suffered from the condition for eighteen years and presented much deformity, treatment was undertaken largely with the idea of testing the limitations of the therapeutic methods employed. The patient gave a history of having had tonsillitis nearly every winter from six to eighteen years of age, though no operation had ever been performed. Her general health had been good, however. Her present trouble began eighteen years ago in the right knee, where she noted a grating and cracking upon flexion. Within a few years her fingers, wrists, arms, and shoulders became involved, and she said that the pain was exquisite.

The disease progressed steadily, although she was treated for two years at the dispensary of the University of Pennsylvania, and had neglected no opportunity to obtain relief. She also was attended for six years or more as a private patient by the same physician who attended her at the dispensary. Two years ago she began treatment at the dispensary of the Orthopædic Hospital,

where she obtained some benefit from baking and Swedish movements, though the course of the disease was apparently not influenced. Through breaking up and stretching the adhesions, etc., she acquired some increase of motion, and her general health was benefited by tonic treatment.

During the two years of attendance at the Orthopædic Hospital Dispensary some days were spent in the ward for closer study.

Examination showed a rather stout and well-developed woman of good color and intelligence. Frequent examination of the ears, nose, throat, and teeth revealed no focus of infection, and the teeth were well cared for. A fruitless search had been conducted for many years on the above basis of infection.

The right shoulder was slightly larger than the left and the bones felt thickened. Passive motion gave distinct crepitus on both sides, and she could not raise her right arm to comb her hair. The elbows showed thickening, crepitus, and limitation of motion. The right knee was enlarged and held flexed to 60 degrees, and the tendons were rigid. Crepitus was marked, and voluntary motion was limited to about two inches.

The arches of the feet were flat, the ankles were thickened, and crepitus was readily felt in them also. There was marked enlargement of the bone ends in the hands and wrists. The fingers were mostly hyperextended and deviated to the ulnar side, though there was also marked flexion and apparent ankylosis in some. In short, the condition was typical of advanced rheumatoid arthritis. The urine was essentially normal. Blood examination showed red-blood cells, 3,550,000; white-blood cells, 9600; hemoglobin, 58 per cent. The blood-pressure was 120 systolic and 80 diastolic, and the body weight 141 pounds.

An *x*-ray examination by Dr. Newcomet showed the colon to be greatly elongated, and sharply bent upon itself at the hepatic and splenic flexures. The stomach was dilated and ptosed, and was divided into an upper and lower pole by the impingement of the bowel. The hands showed marked hypertrophic and atrophic changes (Fig. 1).

On admission she was allowed to eat whatever and as much as she chose of the house diet, and a record was kept of this in terms of table and teaspoons, glassfuls, etc., and when necessary some articles were weighed. A rather close approximation could thus be made of the caloric value of her food by consulting suitable tables.[2] The itemized figures for the respective meals during this period have unfortunately been mislaid, but the sum totals for an average twenty-four hour period are given below: Bread, 6 slices; milk, 3 glasses; egg, 1 glass; oatmeal, 2 tablespoonfuls; sugar, 1 dessertspoonful; potatoes, 2 tablespoonfuls; chicken, 50

[2] Food Values, by Edwin A. Locke, 1911.

grams; spinach, 2 tablespoonfuls; custard, 2 tablespoonfuls. Total about 1662 calories, though she sometimes ate more. Weight, 137 pounds, about. Calories per 1 pound body weight, about 12 or 26 per kilo. While upon this diet, about ten days, she was in much discomfort.

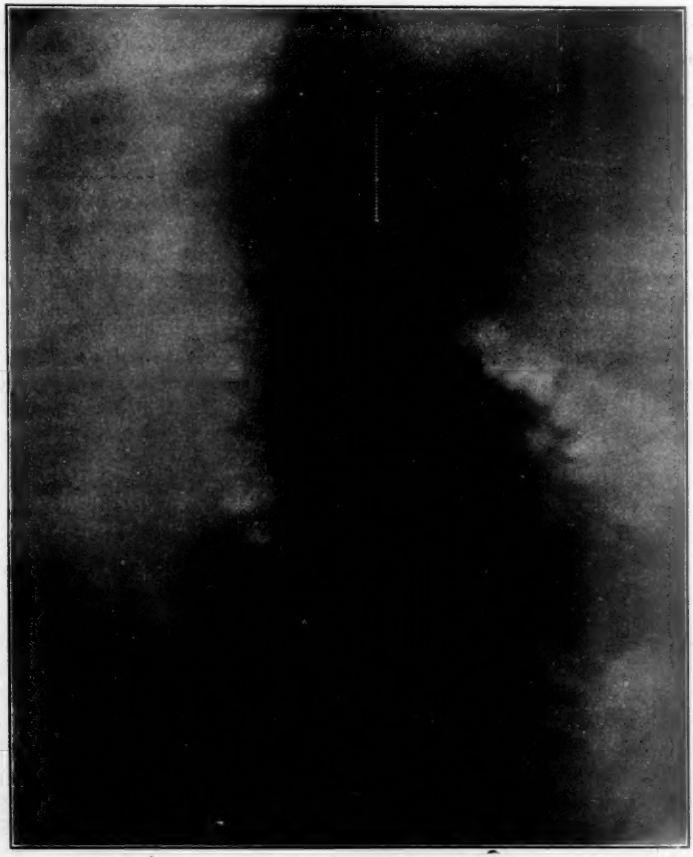

FIG. 1.—Case VIII. Type of elongated and tortuous colon described. The reproduction imperfectly illustrates the condition.

Observations were made in regard to the ethereal, preformed, and total sulphates in the urine and will be mentioned later. This will be designated Period 1.

At the completion of the observations she was placed upon the following:

6.30 A.M.: Milk, 200 c.c.
Breakfast, 1 apple; 1 piece toast; milk, 200 c.c.
10.30 A.M.: Milk, 200 c.c.
Dinner: Milk, 200 c.c.; 3 tablespoonfuls of tomatoes; lettuce (plain with salt).
Supper: Milk, 200 c.c.; 1 piece of toast; 3 tablespoonfuls of stewed fruit.
8 P.M.: Milk, 200 c.c.

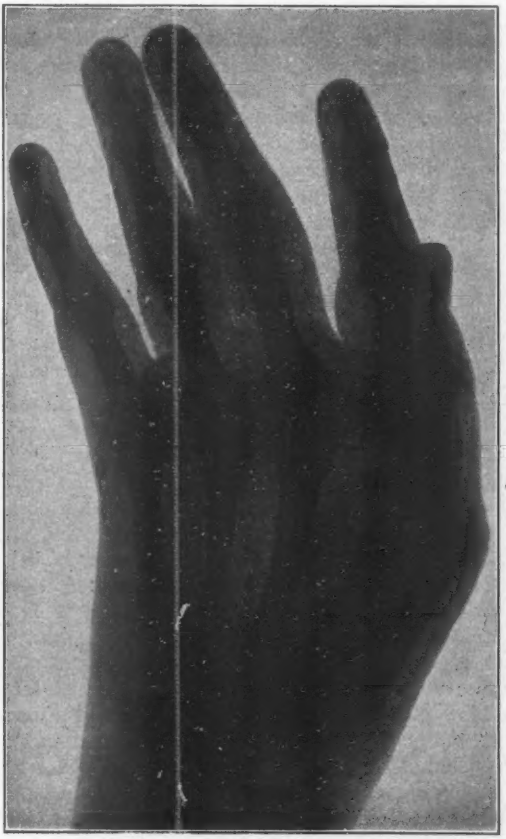

FIG. 2.—Right hand of Case VIII. Before treatment.

This yielded in the neighborhood of 1375 calories or 10 calories per pound of body weight or 22 calories per kilo. This is near the low limit assigned by physiologists.

The additions to and changes in her diet together with the progress of the case were as follows:

February 14, 1913. Lettuce, with salt, at lunch.

February 20. Tomatoes (stewed without sugar), spinach, and stewed celery (no flour) alternated at lunch.

February 23. One soft-boiled egg added at lunch.

February 27. French dressing on salad.

March 12. Soft-cooked egg at breakfast and supper.

March 31. Stopped evening egg and replaced it by a weighed amount of chicken.

April 21. Baked potato of 150 grams, with 5 grams of butter added once a day at lunch, milk, 200 c.c., stopped and 2 tablespoonfuls of 20 per cent. cream added to the milk twice a day.

April 24. Asparagus. Exchanged meat for the egg at lunch.

The daily ward notes here follow:

February 9, 1913. No essential change in her condition since being upon a house diet for three weeks past.

February 13. New diet started.

February 15. Hands seemed somewhat more wrinkled, the skin being loose; there was less pain on pressure. Had pain in right knee, but slept better than she had been sleeping; pain generally awoke her.

February 18. Hands distinctly better. Skin more wrinkled and knuckles showed when a fist was made. Had a good night. Her period was due in two days, but she had no marked increase of pain and malaise as had been her unusual experience. Right knee was a little better.

February 27. Continued subsidence of swelling. Bony parts were more prominent. Fingers were more spindle-shaped. Period long overdue.

March 3. Period arrived in force. Joints felt fairly well.

March 13. Could have the terminal phalanx of her little finger moved passively for the first time in four years. Right knee was easier in walking.

March 22. Could straighten out right elbow for first time in eight years.

March 28. Marked subsidence of left hand especially, and fingers were more tapering. Period now on, and some pain, but less than usual. Felt great relief in the cervical spine as to mobility and pain.

May 21. Except for the ulnar deviation the left hand almost resembled a normal hand, so great had been the subsidence of the soft tissue involvement and the return of function. The terminal phalanx of the little finger of the left hand, mentioned previously as apparently ankylosed in flexion for four or five years, recovered considerable motility some weeks previously. It was found, however, that it could also be straightened to very nearly the

normal position in extension. The patient's improvement had been so great that it was difficult to appreciate the degree of deformity originally present. Every diseased joint had shared in this, though it was more obvious in some than in others.

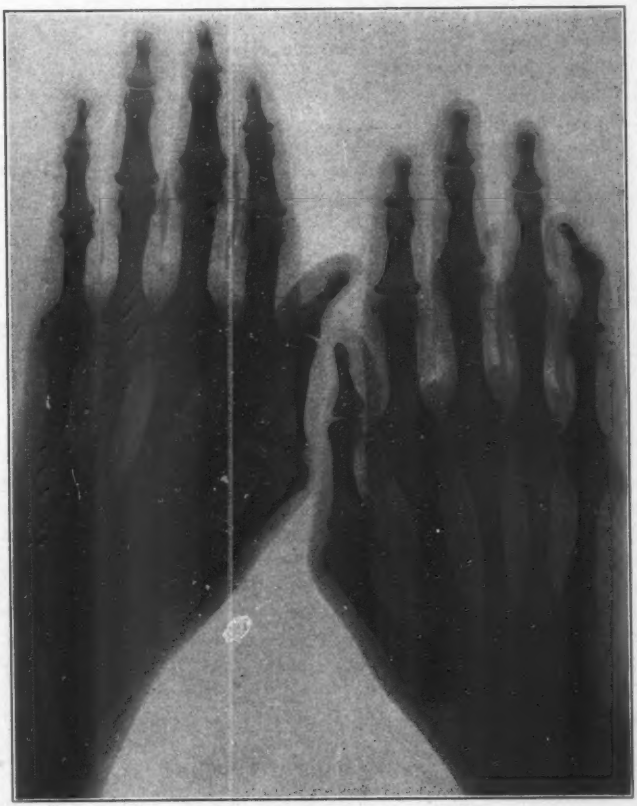

FIG. 3.—Hands of Case VIII. After treatment. Notice lessened ulnar deviation, better position of bones in the metacarpophalangeal and wrist-joints, and the lessened soft tissue swelling of right hand as compared with the earlier picture.

June 8. In excellent shape. Hands were better than in last note.

On May 13 her dietary, etc., was ample, and consisted of the following, as copied from the record of that day. It varied slightly as above indicated in the list of dietary additions and options:

6 A.M.: 1 glass of milk (200 c.c.).

Breakfast: 1 apple, 120 grams; 1 glass of milk; 1 piece of toast, 24 grams; butter, 11 grams; 1 soft cooked egg, 46 grams.

10 A.M.: Milk (200 c.c.), with 2 tablespoonfuls of cream, 20 per cent.

Lunch: Baked potato, 150 grams; butter, 5 grams; roast beef, 70 grams; raw tomato, 95 grams; lettuce, with 1 teaspoonful of vinegar and salt. (She did not care for oil.)

3.30 P.M.: Milk (200 c.c.), 1 glass, with 2 tablespoonfuls of 20 per cent. cream

Supper: Chicken (stewed), 30 grams; 1 slice of toast, 25 grams; butter, 2 grams; 1 glass of hot milk (200 c.c.); 3 tablespoonfuls of unsweetened prunes.

8 P.M.: 1 glass of milk (200 c.c.).

Her weight at this time was 127½ pounds and she still looked needlessly stout. Practically speaking, she was cured, as the gap to be bridged between this condition and complete recovery was trifling especially as compared with that between her present and her original state, and was seemingly a question only of continuing treatment. Marked pressure over her hand joints still elicited some tenderness, and she complained of some scattered pain at times, but both were growing daily less. The patient went out for a walk every day, and she was active in and around the ward. On July 2 she went home, looking and feeling very well, and still progressing.

CASE IX.—Mrs. F. E., aged thirty-nine years, white. Referred by Dr. William B. Cadwalader, of Philadelphia, from the Orthopædic Hospital. This patient was a Russian Jewess, and spoke English imperfectly. Her husband and two daughters were healthy, but her previous medical history was not clearly obtainable. Her present trouble dated back nineteen years to Russia, and began in her hands. The shoulders, knees, and elbows became progressively involved over a period of five years, and had grown worse.

She first had a physician for one year at her home, then went for two months to take the "cure" at Odessa, Russia. She was slightly improved by this, but relapsed.

She again consulted her physician, who advised a return to Odessa for two months, but this was without improvement. She then sought other medical advice, came to America, and for two years remained in *statu quo*, but again gradually grew worse. Three years ago she took treatment for one year twice a week at a private hospital, and had Turkish baths, baking, massage, and (apparently) passive hyperemia. This was of no avail, and about one year ago she went to Mt. Clements, Michigan, and took forty-two baths over a period of two months, but says she felt worse as a result of them.

Physical examination revealed a spare woman, somewhat "hunched up," with her right forearm ankylosed at right angles and her left limited in its motion to one-third the normal range. The right wrist was entirely ankylosed and the left practically so. The arms could not be raised at the shoulders, and the hands

showed great lateral deviation, with marked flexion and rigidity of nearly all fingers, though they presented relatively little soft tissue swelling. The synovial sacs of the joints were distended, but the periarticular tissues were so slightly swollen that it seemed that improvement would be difficult of observation until well under way. Her knees and feet were also enlarged and deformed though she was able to walk.

The urine was essentially normal, and the indican reaction was persistently negative. Blood examination showed red-blood cells, 4,420,000; white-blood cells, 10,100; hemoglobin, 60 per cent. The blood-pressure was 112 systolic and 70 diastolic. The heart and lungs were normal.

The *x*-rays showed the colon to be very long, with the transverse portion ptosed and tortuous. The hands showed chiefly great atrophic and absorptive changes, with some slight hypertrophy.

Upon admission to the hospital she was placed upon the house diet to determine her accustomed food intake, which was found to be about 2053 calories or 20.3 calories per 1 pound of body weight or 44.7 per kilo.

March 9, she was placed upon the following diet:

6 A.M.: 1 glass of milk, 200 c.c.

Breakfast: 1 egg; 1 glass of milk, 200 c.c.; one-half slice of toast; butter, 10 grams.

10.30 A.M.: 1 glass of milk, 200 c.c.

Dinner: Milk, 200 c.c.; spinach, 2 tablespoonfuls.

3.30 P.M.: Milk, 200 c.c.

Supper: One-half piece of toast; lettuce; milk, 200 c.c.

8 P.M.: Milk, 200 c.c.

This yielded about 1375 calories or 14 calories per pound of body weight or 31 calories per kilo. Her weight was 100 pounds.

The additions to and changes in her diet were as follows:

March 17, 1913. One soft-boiled egg at each meal.

March 20. Stopped egg at lunch and supper.

March 21. Stopped milk at 6 A.M. and added 2 tablespoonfuls of cream to the milk at 10 A.M. and 3 P.M. Weight, 98 pounds.

April 4. Stopped milk at 8 P.M.

April 22. Added one-half slice of toast and 2 grams of butter at lunch.

April 25. Added tea, f℥j,[11] with sugar, ℥ij, and 20 per cent. cream, f℥iv, once daily; baked potato, 150 grams, with 5 grams of butter once daily; stopped 1 glass of milk.

April 27. Added 15 grams of butter daily.

May 3. Added 1 apple at breakfast and supper.

May 18. Patient's diet was as follows:

[11] Since many of the ward directions were more conveniently given in tea- and tablespoonfuls, their familiar equivalents in f℥ and f℥ were sometimes used.

Breakfast: 1 soft-boiled egg, 50 grams; 1 glass of milk, 200 c.c.; ½ slice of toast, 15 grams; butter, 2 grams; apple, 100 grams.

Dinner: 1 cup of weak tea made thus: f℥j of tea, with f℥iv of 20 per cent. cream and ℥ij of sugar (two teaspoonfuls), balance of hot water; ½ slice of toast, 15 grams; 3 tablespoonfuls of tomato; roasted potato, 150 grams; butter, 20 grams.

Supper: ½ slice of toast, 15 grams; butter, 2 grams; lettuce, with 2 tablespoonfuls of French dressing (one part of vinegar to three parts of oil); 3 tablespoonfuls of unsweetened prunes (or other cooked fruit); 1 apple, 90 grams.

March 13. Diet started March 9. Had considerable pain at night. Made little complaint.

March 14. Better night.

March 16. Apparently definite signs of improvement in laxity of joints, depressions over joints, and freedom of movement (active and passive) of small joints.

March 17. Could reach her head with her left hand. This was impossible for three months before. First finger of right hand could be better abducted. One egg added to lunch and supper.

March 20. Had three eggs for three days. Improvement very doubtful, though tendons on back of hands seemed to stand out better. Seemed to make better progress on lower diet. Stopped two eggs.

March 21. Not well and having pain. Joints no better. Stopped one glass of milk and added two tablespoonfuls of cream to 10 A.M. and 3 P.M. milk.

March 26. Much improved. Distinct laxity and mobility of joints.

April 2. Had sharp tonsillitis, with fever, Better, but still some fever. Hands showed improvement. Were stiff and painful during her febrile period.

April 4. Still had fever and much pain. No great change in joints, though slightly in direction of improvement. Given aspirin, gr. xv, at once, and in two hours, and then gr. x every four hours for relief.

April 5. Had relief from the aspirin. No other change.

April 6. Fingers better. Temperature normal. Aspirin stopped.

April 7. Could move her shoulders better, and also straighten out her hands. Temperature was normal, but recent "grippe" had caused her to lose weight. Not getting aspirin, and is very happy.

April 8. Better than at any time yet. "I feel fine." Moved shoulders and moved and supinated forearm better than for three to four months. Almost no pain in knees, and felt better.

April 10. Stiffer in elbows and knees, though both moved. Was well on previous day.

April 21. Steady improvement. Whole personality had grown brighter. Hands could be considerably straightened.

April 24. Felt well and wanted to get up.

May 3. Added one apple to breakfast and to supper. Doing very well.

May 8. Very well previous day. Felt stiffer, as did several other joint cases in the ward, coincidently with a change in the weather. Slight swelling of feet on previous day. Slightly better. Had pain in muscles of back in the night.

May 11. Much better. Was doing very well.

May 16. Thought she had been stiffer at night lately and had more pain then. Joints showed only improvement on inspection, however.

It was difficult in this case to differentiate between the pain due to contractured tendons and that of joint disease *per se*. She complained greatly of pain, especially at night, though objectively she seemed to improve. Her diet had been decreased and increased at various times until, on June 19, she received the following, with slight daily variations:

Breakfast: 1 egg; toast, 18 grams (½ slice); 1 glass of hot milk, 200 c.c.; butter, 2 grams.

10 A.M.: 1 glass of milk, 200 c.c., with 1 tablespoonful of 20 per cent. cream.

Dinner: 1 baked potato, 150 grams; turnips, 3 tablespoonfuls, or some other green vegetable as noted elsewhere; 1 tomato; 1 cup of weak tea, with 1 tablespoonful of 20 per cent. cream, and 1 teaspoonful of sugar; butter, 20 grams; 1 apple.

4 P.M.: Milk, 200 c.c., with 1 tablespoonful of 20 per cent. cream.

Supper: Toast, 15 grams (½ slice); butter, 2 grams; unsweetened stewed fruit, 3 tablespoonfuls; hot milk, 1 glass, 200 c.c.; lettuce, with 1 tablespoonful of French dressing, 1 to 3.

Her complaint of pain was so persistent that her diet was reduced on June 23 by stopping the potato and butter at dinner and the milk at 10 A.M. and 4 P.M. On June 25 and 26, the pain was distinctly less. On June 28 it was noted that she walked better than at any time to date, and she said that she could comb her hair and dress herself more easily than she had been able to do for some time. Her joints felt well and limber, but the muscles felt sore from calisthenics and passive movements.

This was one of the most difficult cases to handle. The duration of her illness, nineteen years, the advanced degree of contractures, the intensity and frequency of pain, often made her progress seem slow or doubtful, even though the objective signs were favorable. As in some other cases, the disease eventually was apparently arrested, and the problem became one largely of the mechanics of the joints.

On July 1 she was practically free from pain, her only complaint being that she wanted more food, and was discharged, with in-

structions to continue her exercises and keep to her diet. She could attend to all her wants in dressing and every-day acts.

It will be seen that this case represented the most advanced and longest standing type of the disease, and was deliberately treated as a test. To undo the structural injury of so many years was of course impossible, the idea being to determine whether the disease was amenable at all when so firmly established. It was plain that it could be arrested, but only at a low level of food intake, as the gaps in the "metabolic chain" become perhaps wider after long duration. The patient grew restive under a low dietary, and on returning home she was reported to have considerable discomfort.

CASE X.—Miss H., aged twenty-four years, nurse—attendant at the Country Home for Convalescents of the Presbyterian Hospital of Philadelphia. She presented a history of having had an attack of rheumatic fever when aged thirteen years, at which time many joints were involved, and she was ill for two months. Practically every winter since then she had had, between December and February, a recurrence of rheumatism, especially in her knees and ankles. At these times the joints were painful and usually swollen. The attacks lasted from two weeks to one month, though pain in the joints was noticed for weeks afterward.

The patient had an attack of tonsillitis when aged ten years, and in 1911 an outbreak of rheumatism following the latter.

Since January, 1911, she had had more or less persistent pain and grating in both ankles at all times.

Physical examination revealed a slight goitre, unassociated with tachycardia, exophthalmos, tremor, cardiac hypertrophy, or nervousness, which had been present and constant in size for many years.

The phalangeal joints of her hands were slightly enlarged. The left ankle was tender on pressure, and active or passive motion of either the right or the left ankle gave a slight grating which could be heard and felt. Blood and urine were normal. Weight on admission to the hospital was 101½ pounds in her night-dress.

The *x*-ray examination showed the colon to be elongated and sharply flexed at the hepatic and splenic flexures. The hands showed slight but definite hypertrophic and atrophic changes. The patient's best weight had been 115 pounds.

On November 19, 1912, she was placed tentatively upon a slightly modified diet, as follows:

Meat for dinner only and in very moderate amounts. No potatoes or rice and very little bread; six glasses of milk per diem, distributed at 6 A.M., breakfast, 10.30 A.M., lunch, 3.30 P.M., and at supper. Green vegetables were allowed *ad libitum*. Her weight was 109½ pounds in her clothes.

The notes made in the Presbyterian Hospital dispensary, which she attended, were as follows:

January 8, 1913. Was on night duty and lost nearly two pounds. Took cascara at night, as she was rather costive. Had no rheumatism at all, and had not been free from it for so long a period during the past year. Diet at this date: 6.30 A.M., 1 glass of milk. 8 A.M., breakfast, 1 glass of milk, 1 small slice of toast, 1 egg or small amount of fish or scrapple or (rarely) hot cakes. 10.30 A.M., 1 glass of milk. Dinner, 1 P.M., clear soup, 1 glass of milk; meat in moderation, green vegetables, no rice or potatoes. Custard or junket or wine jelly for dessert, but no bread or rice or flour puddings. 3.30 P.M., 1 glass of milk. Supper at 6 P.M., 1 glass of milk, lettuce, stewed fruit, or jelly; occasionally a small amount of scrambled egg. Weight now 108 pounds.

January 22. Beginning ten days previously and until the day before had pain in ankles, shoulders, knees, wrists, and right elbow. Weight, 108¼ pounds. Desserts and meat at dinner were stopped Advised to rest one hour in morning and afternoon.

January 28. Much better, except that her feet were not much improved. Tongue clean. Bowels open. Weight, 108¼ pounds.

March 5. Feeling "fine." Two weeks before, patient had some pain and stiffness in the left shoulder for one day and one night. The proximal point of the third finger of the left hand was slightly stiff off and on for several days at the same time. She had been entirely free from headache for six weeks; formerly was subject to it oftener than that.

March 17. Ten days previously had a bilious attack, with vomiting, and began to have pain in right wrist, thumb, and two fingers. Patient was given two doses of aspirin, each ten grains, by the resident physician, before consulting the writer after which her diet was ordered somewhat reduced, and she was put to bed and given calomel and salts. She had no other antirheumatic or analgesic medicine, and after four days in bed, where she was kept to avoid undue tissue loss during the low dietary, she went back on duty and had been active and "feeling fine" for four days.

April 18. Apparently perfectly well, and had been on night duty for a month or more. Weight, 106¾ pounds. Was not taking medicine of any kind.

June 18. Patient was sent for and found to be feeling well, performing the regular hospital duties, as she was also on July 1.

(To be continued.)

REVIEWS

ANATOMY, DESCRIPTIVE AND APPLIED. By HENRY GRAY, F.R.S., Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. New (American) edition, thoroughly revised and re-edited, with the ordinary terminology followed by the *Basle Anatomical Nomenclature* by EDWARD ANTHONY SPITZKA, M.D., Director of the Daniel Baugh Institute of Anatomy and Professor of General Anatomy in the Jefferson Medical College of Philadelphia. Pp. 1502; 1225 illustrations. Philadelphia and New York: Lea & Febiger, 1913.

THE new American edition of *Gray's Anatomy*, representing the ninteenth edition, will unquestionably be welcomed by a large proportion of the students and teachers of this subject. For half century or more the work, both in the original and the many succeeding editions, has been held in high repute as a thoroughly practical treatise.

In comparing this edition with the preceding one which was published in 1910 no very great changes will be noted. About 20 or 25 new illustrations have been added, a few unessential details eliminated and only such additions made as were necessary to represent the recent anatomical advances. Many points may be cited in praise of the book. Every effort has been made by both the eminent revisionist, Dr. Spitzka and the publishers to make the book fulfil every requirement for which it was intended and to maintain the high standard which has characterized the book in the past. The subject of human anatomy is presented in as broad a manner as possible without endangering its usefulness as a text-book for the student. The text throughout is clear, concise, systematic and the abundant use of superb illustrations, in colors, cannot fail to be appreciated by the reader. A good feature of the illustrations is the printing of the names of the parts directly on them. It assists one in remembering the location and relations. Recognition of the increasing use of the Basle Anatomical Nomenclature has been indicated by following the ordinary terms which are familiar to American students with the B.A.N. terms in parenthesis. The new terms are also italicized in the index.

The sections on osteology, syndesmology and myology are very thorough; the illustrations of the first mentioned section have the muscular attachments outlined in red and those of the capsular

ligaments in blue. The description of the muscles is facilitated by plates showing the attachments in red and the insertions in blue. Much space has been devoted to the consideration of the vascular systems which are given in detail. The nerve system is carefully and faithfully described and the practical manner in which it is presented will materially assist the beginner in acquiring a knowledge of the rather intricate morphology of the central nerve system. A more detailed description of the course of the superficial nerves would be an improvement and of great help to surgeons who are desirous of using Kocher's method of conduction anesthesia or the "nerve-blocking" method advanced by Dr. Cushing. Greater knowledge of the nerves, for many reasons, is becoming more and more of a necessity to the surgeon and it is a noticeable fact that nearly all of the present day text-books are deficient in this regard.

The organs of special sense, digestion, respiration and of the uro-genital system are described in a complete, comprehensive manner and the text is free of obscure or perplexing passages. Instructions for dissecting are given at intervals throughout the book, and while very meager will be of use to the student.

Histology and embryology are considered briefly, short accounts only being interpolated in connection with the gross anatomy of the various structures. Under the title of Applied Anatomy many surgical and medical conditions are discussed, and while helpful otherwise emphasize the importance of a thorough, practical knowledge of anatomy in the practice of modern medicine and surgery.

All things considered this edition is a decidedly attractive one and will probably meet with even greater demand than its predecessor. H. D. L.

A Manual of Otology. By Gorham Bacon, A.M., M.D., Professor of Otology in the College of Physicians and Surgeons, Columbia University, New York. New sixth edition. Pp. 536, 164 engravings and 12 plates. Philadelphia and New York: Lea & Febiger, 1913.

Dr. Bacon's *Manual of Otology*, now appearing in its sixth edition, is well deserving of its popularity, as it contains more concise information about the ear than any other work of its size and character. It is undoubtedly the best known manual of diseases of the ear in America, and the present edition is well edited, with many sections rewritten and enlarged, while new ones have been added to keep pace with the growth of knowledge in otological subjects since the last edition appeared. So well known is the book that it hardly seems necessary to go into its merits in

great detail. There are, however, some particulars in which the reviewer feels that it could be still further improved.

The sections on the anatomy and physiology of the ear are well written for the most part and clear; well illustrated with schematic drawings and photographs of gross temporal bones and histological sections. At the present time, when the labyrinth is so much under discussion and so much research work is being done on its physiology, it would seem that the description of its anatomy, difficult for a tyro to understand at the best, might be clarified and simplified.

Excellent are the illustrations throughout, the well-known ones being supplemented by many new ones, mostly photographs of actual specimens. In this connection it would seem that the modern custom of putting in plates of sets of instruments necessary for a given operation might well be changed and the space taken up with these somewhat useless illustrations, used for more text.

Dr. Bacon's admirable conservatism is apparent throughout the book, which is brought up-to-date by the addition of the lastest knowledge of labyrinth reaction tests and operative procedures. This latest edition deserves, as all previous editions have deserved, its rank as a standard manual and should be on the shelves of every practitioner of medicine who wishes condensed information on diseases of the ear. G. M. C.

MINOR AND OPERATIVE SURGERY, INCLUDING BANDAGING. By HENRY R. WHARTON, M.D., Surgeon to the Presbyterian Hospital, Children's Hospital, Consulting Surgeon to St. Chistopher's Hospital, etc. Eighth edition; pp. 700; 570 illustrations. Philadelphia and New York: Lea & Febiger, 1913.

THE fact that this work has reached its eighth edition is evidence of its popularity. The greater part of the text is accurately to the point and gives the desired information in the shortest space possible. However, at times the author wanders aside from his chosen field into the realms of bacteriology and literature. Again, some of the simpler elementary subjects are dealt with a little too exhaustively; a good point, however, if not carried too far. On the other hand, there is no mention of some important minor subjects, such as the technique to be followed in the search for a foreign body in the soft parts.

The illustrations are very numerous. It should be noted, however, that several of the illustrations of bandages are incorrectly drawn by the artist; a point of importance only from a student's standpoint.

In the operative chapter the author has treated as minor procedures a number of operations that are generally conceded to be

major work, such as nephrectomy, ureter surgery, pyloroplasty, etc. Such minor procedures, however, as removal of a sebaceous cyst, or a foreign body under the nail are not mentioned. Aside from these criticisms, which are perhaps largely a matter of individual opionion, the work has many good points and in the future, as in the past, will doubtless prove of value to many. E. L. E.

THE SURGICAL CLINICS OF JOHN B. MURPHY, M.D., at Mercy Hospital, Chicago, August, 1913. Vol. II, No. 4; Pp. 104; 50 illustrations. Philadelphia: W. B. Saunders Co., 1913.

THIS number opens with a paper entitled "Some Observations on Vaccine and Serum Therapy from Dr. Murphy's Clinic," by Philip H. Kreuscher, M.D., of Dr. Murphy's Staff. The paper was read before the South Side Branch of the Chicago Medical Society, May 27, 1913, and it is followed by the discussion which took place when the paper was read, participated in by Dr. Charles L. Mix, Dr. T. L. Dagg, Dr. J. L. Miller, Dr. L. Hektoen, and Dr. Murphy himself. Dr. Murphy's views on the subject are further expounded in two clinical lectures delivered at Mercy Hospital during the following week. The entire discussion on vaccine and serum therapy thus occupies a space of 35 pages. The conclusion of the whole matter seems to be that in acute infections the use of sera is more efficacious than is that of vaccines, because the patient is thus supplied with ready-made antibodies; but in chronic infections, where there is time to stimulate the patient's own powers of antibody production, vaccines may prove of considerable benefit, especially if the infecting organism is known. Dr. Murphy and his staff have used them chiefly in cases of chronic joint disease, and their beliefs are thus stated by Dr. Mix: "From the date of the original infection and the date of the appearance of the metastases in the joint, the physician may be able to name the germ. Recall, for example, typhoid fever—when do the joint disturbances begin? In the third or fourth week. When do the joint disturbances after the period of acute infection in gonorrhea begin? In our experience the joint becomes infected only between the eighteenth and the twenty-second day. When do the joints become infected in the streptococcic infections? In our experience the second or third day. Each of the germs more commonly at fault in the joint infections has a definite time for infecting the joint after the primary infection" (p. 561). It is further stated by Dr. Mix that where the infecting organism is not known, "mixed vaccine therapy is in accordance with common sense:" but Dr. Hektoen (p. 565) cautiously says "as regards the use of mixed

vaccines, it does seem to me that we ought to proceed very slowly and very carefully. It may be perfectly proper to use mixed vaccines, provided we are certain we have a mixed infection."

There is next presented a series of ten radiographs of the larger joints of the body (most of them shown in two planes) made after injecting the arteries with a red-lead emulsion. Professor Ranson of the Department of Anatomy of the Northwestern University Medical School made the cadaveric preparations, the skiagraphs were made by Dr. George W. Hochrein "who does all the radiographic work for Dr. Murphy," and the illustrations were properly labeled with the names of the arteries and their branches by Mr. Sumner Koch, an assistant of Professor Ranson. These illustrations are of great interest and considerable value, though the injected vessels naturally appear to lie all in one plane.

The main bulk of the volume is made up, as usual, of clinical talks by Dr. Murphy, covering a wide range of topics, in which bone surgery holds the most important place. But the concluding article (for it is not a clinical lecture, nor has it "never appeared in print before") is on appendicitis, or rather "On early operation in perityphlitis," being an abstract of a paper published by Dr. Murphy, February 26, 1890; it is "reprinted to show striking similarity between Dr. Murphy's teaching of today and that of twenty-five years ago." For all of this let us be duly thankful.

A. P. C. A.

SYPHILIS AND THE NERVOUS SYSTEM. By MAX NONNE, Chief of the Nervous Department of the General Hospital, Hamburg. Authorized translation from the second revised and enlarged German edition by CHARLES BALL, M.D., Chief of the Nervous and Mental Department of the St. Paul Free Dispensary. Pp. 406; 98 illustrations. Philadelphia and London: J. B. Lippincott Company, 1913.

IT was a happy idea which caused Dr. Ball the translator, to bring to the English speaking physicians Nonne's excellent book on syphilis and the nervous system, for there is no one physician who has had such wide opportunities nor is there one who has had more skill and aptitude for this kind of work than he. Perhaps there is no division of medicine which is undergoing such changes so far as classification is concerned than the specialty of nervous diseases and a large part of it is due to the fact that we are gradually recognizing that many more diseases of the nervous system are due to syphilis than we originally thought. In the recognition of syphilitic diseases of the nervous system the greatest help has been the so-called four reactions of Nonne, the author of this book.

The present problem deals not so much with the clinical phases of the subject, as with the question of whether we should continue the old classification of meta-syphilitic diseases, and their therapy. Nonne in a recent paper before the International Congress in London took the attitude that we are unable at the present moment to say definitely what is a meta-syphilitic disease and what is not, and the only thing we can definitely say is, that syphilis causes this and that disease, and that the best thing to do is to wait and see what further advances will teach. As far as the therapy is concerned, he states that he is not as hopeless regarding the therapy of tabes as others are, for he himself has seen four cases in which the Argyll-Robertson pupils have disappeared under mercury and salvarsan. The reviewer can only repeat that this is the best book on syphilis of the nervous system and the translator has done his work well. T. H. W.

TEXT-BOOK OF GENERAL AND SPECIAL PATHOLOGY, FOR STUDENTS AND PRACTITIONERS. By HENRY T. BROOKS, M.D., formerly Professor of Pathology at the New York Post-Graduate Medical School and Hospital. Pp. 1127; 525 illustrations (110 in colors) and 15 plates in colors. Philadelphia: F. A. Davis Company, 1912.

THIS book was started as a translation of Langerhans "Grundriss der Pathologischen Anatomie," but advances in the science and the death of the German pathologist caused the author to adopt another method in the preparation of his book. The work is intended to follow the pathological physiology through the various evidences of disease, physical changes being traced as evidence of these altered processes. The book is not a physiological chemistry but the metabolic reasons for the pathological states are emphasized. Minute pathology is more extensive than the gross which is given in a sketchy manner. The author aims at assisting the student and the physician in the interpretation of clinical conditions. The first half is devoted to the broad principles of pathology, the second half to special organs. In the first part considerable attention is given to peculiar manifestation of the different diseases in special organs. Similar treatment is found under inflammations. The chapters on immunity and on the eye are by collaborators. The latter is, in length, out of all proportion to the rest of the book occupying 150 pages while the vascular system is accorded less than 40. The result is, however, a fairly complete, condensed, and readable pathology of the eye, a thing uncommon in most one-volume general pathologies. The method of spelling all adjectives and adverbs such as clinical and clinically without the "al" seems to the reviewer to be not wholly advisable. "Clinic" and "clinicly"

are especially awkward. The illustrations are mostly copied and the one-toned colored pictures are sometimes indistinct. The schematic originals intended to show certain physical relations of disease are much better. The English reads easily except for the form of adjectives noted above. On the whole, in spite of the large number of general pathologies that already exist, the book should prove of value. H. F.

TEXT-BOOK OF OBSTETRICS. By BARTON COOKE HIRST, M.D., Professor of Obstetrics in the University of Pennsylvania. Pp. 1013; 895 illustrations. Philadelphia and London: W. B. Saunders Co., 1913.

VERY little that is new has occurred in obstetrics since the previous edition, but those procedures that have any bearing upon modern obstetrics are embodied in this work. The author is most enthusiastic about the close relationship of obstetrics and gynecology, and many so-called gynecological operations are described in detail. The physiology of the process of generation precedes the pathology, except that sterility is taken up in connection with normal conception and malpositions, and presentations are studied with the mechanisms of labor. The pathology of the breast is treated more fully than in the previous edition; especially is this true of malignant disease. There are also many new illustrations which aid mate rially in teaching. The author comments more favorably in this edition, upon extra-peritoneal Cesarean section, and thinks its field has enlarged. It is generally believed, however, that suspect and infected cases had best not be subjected to any method wherein the uterus is opened, intra- or extra-peritoneally, and allowed to remain after the child is removed.

The author's practice of delaying repair of a primary laceration of the perineum until the end of the first week, has not met with the approval of the majority of obstetricians. A second etherization and disturbance of the patient just when conditions are resuming the normal, seem unwarranted, when one considers the good results obtained by an immediate repair.

The author has commented freely upon the newer ideas in obstetrical teaching, such as the use of the active principle of the pituitary gland in uterine inertia, the significance of the changes in blood pressure in toxemias, serum therapy in puerperal infections, the inadvisability of doing hysterectomy in early puerperal infection, and the excision of thrombosed pelvic veins. His teaching on all these subjects is conservative and sound. The work is most readable, the subjects are disposed of in a clear, concise, and up-to-date manner, equally valuable to pupil and general practitioner. E. P. B.

DISEASES OF THE EYE. A HANDBOOK OF OPHTHALMIC PRACTICE FOR STUDENTS AND PRACTITIONERS, By G. E. DE SCHWEINITZ, A.M., M.D. Professor of Ophthalmology in the University of Pennsylvania, and Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to the Philadelphia Polyclinic; Ophthalmic Surgeon to the Philadelphia Hospital; Ophthalmologist to the Orthopedic Hospital and Infirmary for Nervous Diseases. Seventh edition; pp. 979; 360 illustrations and 7 plates. Philadelphia and London: W. B. Saunders Co., 1913.

IN the twenty-one years that have elapsed since its first appearance, there have been seven editions and several reprints of de Schweinitz's treatise. This shows clearly what the profession thinks of it. It is not too much to say that it is the American text-book *par excellence* and will hold its own with any similar work in any language. A complete and well arranged index of 56 pages adds to the value of the book.

The present edition differs from its predecessors in careful revision of the subject as a whole, and in the addition of such recent contributions as are likely to obtain a permanent place in ophthalmology. These include, among others, a short description of the tonometer, particularly that of Schiötz, to replace the finger test which is declared to be neither a safe nor an accurate procedure; Hertzell's diaphanoscope and the manner of using the same is described, together with the appearances it gives of the interior of the eye, especially in connection with orbital and sinus disease. Elliot's operation of trephining of the sclera in glaucoma is summarized, as is also Toti's operation in disease of the lacrimal sac, and Reese's muscle resection operation. Recent descriptions of certain ocular affections, such as sporotrichosis, Widmark's conjunctivitis, blue sclerotics, von Hippel's disease, etc., are alluded to.

Salvarsan and neosalvarsan are highly recommended in syphilitic iritis; the author's experience has shown excellent results from the administration of gonococcic vaccine in gonorrheal iritis, which form the writer has found much more common than has usually been supposed, this being the origin in many instances of so-called rheumatic iritis.

Of the Smith or Indian method of extraction of cataract in the capsule, the author quotes a brief description; he gives it as his impression "that while this operation may have a place in ophthalmic surgery, especially in the extraction of unripe cataracts, it is not likely to drive from the field those procedures which have for years been firmly and favorably established."

As the reviewer stated upon the occasion of a review of an earlier edition of this work, this hand-book is an entirely reliable and satisfactory account of the present position of ophthalmic science.

As pointed out by Hirschberg, it has a certain advantage over larger and encyclopediac treatises, in that it is practically the outcome of a single mind, "von einem Guss." It has another quality by no means always found in scientific, particularly medical, writing: the style is precise and clear and makes easy reading, and we know from an eminent writer that "easy reading is hard writing."

The work will no doubt continue to meet with the same cordial reception which has been accorded to its predecessors.

T. B. S.

PATHOLOGY. A MANUAL FOR TEACHERS AND STUDENTS. W. T. COUNCILMAN, M.D., Shattuck Professor of Pathology, Harvard Medical School. Pp. 405. Boston: W. M. Leonard.

THIS manual is an extension of the syllabus of Pathology published by Councilman and Mallory in 1904 and is designed with special reference to the teaching of the subject. Illustrations are purposely omitted to encourage the student to make his own illustrations from actual specimens and for this purpose, in addition to the 405 pages of text, 263 blank pages are introduced at the end of the various chapters. There is considerable difference in the fulness with which different subjects are discussed. Inflammation and repair are treated rather completely. The entire subject of tumors is covered in 40 pages. Under the infectious diseases the lesions usually resulting from twenty-four of the commoner organisms are described, occupying in all 135 pages. To parasitic worms 4 pages are given. The pathology of the kidneys is considered at especial length. The classification of the nephropathies is exceedingly clear and simple and emphasizes the histologic rather than the gross changes in these organs. On the other hand, the discussion of hepatic conditions, notably the cirrhoses, is very brief and incomplete. The author states that the variation in the space allotted to various subjects is not meant as an index of their relative importance, but that fuller description is given to those conditions which illustrate principles of wide application. Following almost every chapter is a description in outline of experiments which the student may perform, illustrating the principles and conditions that have been studied. This feature of the book, comprising in all about 50 different experiments, has been prepared by Assistant Professor Karsner and adds much to its value. After the discussion of the special pathology of each system and of each of the common infectious diseases the author has added full illustrative autopsy protocols, sometimes with the clinical history of the case. These protocols, of which there are 54 in all, are followed by a few critical remarks. The book seems to us to be exceptionally well adapted to the purposes for which the author intended it.

J. H. A.

THE TREATMENT OF DISEASES IN CHILDREN. By G. A. SUTHERLAND, M.D., F.R.C.P., Physician to Paddington Green Children's Hospital. Second edition. Pp. 403. London: Henry Frowde, Hodder, & Stoughton, 1913.

THE book is designed as a practical guide in treatment for the young practitioner. The necessary descriptions of the various diseases are concise, conservative, yet contain all the facts that may be safely accepted or the most plausible theories in lieu of facts. The author wisely adopts the plan of describing in full one definite line of treatment rather than enumerating long lists of remedies or measures which have attained more or less reputation as cures in the diseases discussed. The chief impression upon reading the book is that it is written by a pediatrician of sound views and admirable common sense, who knows whereof he writes. For example, the results of a careful personal observation of over 100 cases of orthostatic albuminuria are worthy of careful attention. The book, therefore, represents a real addition to the knowledge of practical treatment, not merely a skilful compilation of heterogeneous opinions.

It will suffice to point out the comparatively few instances where his teaching differs from that of most American authors. The dosage of some drugs is larger than we usually accept as desirable. The diet provided for patients with typhoid fever falls far short of average caloric requirements and is distinctly less than modern American practice accepts. The open air treatment of cases of marasmus with subnormal temperature, is being replaced in many American hospitals by the use of superheated rooms, with results which scarcely permit of doubt as to their efficacy. In the matter of general dietetics, it often seems that English children are more fortunately equipped, in a gastronomic sense, than their American cousins. Certain it is that the most conservative English pediatricians are more liberal in feeding children than their American confrères, while their precaution in the use of flannel "next to the skin," during the summer, in such diseases as rickets, must be due to climatic conditions as well as to conservatism. The suggestion that the superfluous fat seen in many rickety babies tends to prevent free cutaneous circulation and should be reduced by restricting carbohydrates in the diet, has much to recommend it. Another suggestion, new to the reviewer, is that cases of chronic intestinal indigestion and marasmus, bottle-fed, should receive the benefits of a variety in the twenty-four hours diet; for example, milk mixtures by day and whey at night. Finally the author's views on quaratine in diphtheria will strike a sympathetic chord in the minds of many of his readers. He believes that the persistence of positive cultures four to eight weeks after the inception of the disease—depending upon the type of case—should not restrict the patient to the trying conditions of strict quarantine. J. C. G.

DISEASES OF THE STOMACH AND UPPER ALIMENTARY TRACT. By ANTHONY BASSLER, M.D., Professor of Clincial Medicine, New York Polyclinic Medical School and Hospital. Second edition. Philadelphia: F. A. Davis Company, 1913.

THE compliment of a large first edition exhausted in the first year of publication is almost sufficient in itself to make a review of their book unnecessary.

The work is an exhaustive treatise on diseases of the stomach and the upper alimentary tract, based on facts that have been derived from many years of clinical observation in public and private practice re-inforced by much first-hand laboratory knowledge of the safe and sane kind.

The essential anatomy and histology of the tract is thoroughly covered; there are helpful suggestions regarding the importance of careful history taking and the keeping of permanent records; the sections on etiology, pathology, symptomatology, and diagnosis are clear-cut, comprehensive, and readable, and the several chapters devoted to a discussion of the different forms of treatment, by diet, drugs, waters, electricity, and other physical therapeutic measures, are especially good. For the man doing special work along gastro-enterological lines and for medical students this book can be recommended as one of the best on the subject in the English language within the reviewer's knowledge. B. B. V. L.

THÉRAPEUTIQUE USUELLE DU PRACTICIEN TRAITEMENT DE LA TUBERCULOSE. By ALBERT ROBIN, Professeur de Clinique, Therapeutique a la Faculté de Médecine de Paris. Third Series; Pp. 640. Paris: Vigot Freres.

ONE approaches with considerable hesitancy a volume of such length on the treatment of tuberculosis, fearing lest in the obvious detail of the many important subheadings the author may have failed to preserve perspective and proportion.

In this work the first fifty pages lead one into such a chaos of chemical and metabolic inaccuracies that one's fears are confirmed and further reading made difficult. It is scarcely necessary to add that the clinical chapters are filled with references to such delightful fictions as the "co-efficient de robusticité de Pignet" and a classification of the liver conditions due to tuberculosis into twelve subdivisions. In the sections which are truly concerned with treatment, every method good or bad is discussed in full. Twenty-five pages are devoted to the cure of tuberculosis by mineral waters, and the serum of Marmoreck receives undue consideration.

The book, as a whole, is distinctly verbose and unscientific, and is a representation of the worst faults of French medical writings. O. H. P. P.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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On the Infectivity of the Milk of Syphilitic Women.—P. UHLENHUTH and P. MULZER (*Deutsch med. Woch.*, 1913, xxxix, 879) have succeeded in demonstrating experimentally the presence of Treponema pallidum in human milk. Of 8 cases studied, positive results were obtained in 2. The milk used in the experiments was sucked from the breasts by means of a Bier cup, the nipple and breast having been previously cleansed with bichloride of mercury. The milk was then injected into rabbits' testicles. P. Uhlenhuth and P. Mulzer emphasize especially the importance of the finding of spirochetes in the milk of the mother of a syphilitic child, the mother being free from symptoms (latent syphilis). The mother's blood gave a positive Wassermann reaction, and they also succeeded in demonstrating the presence of the spirochetes in the blood of a similar case. These facts, therefore, demonstrate the danger of accepting a woman as wet-nurse to non-syphilitic children. The absence of symptoms does not mean that a syphilitic is in a non-infective stage of the disease, and all possible means should be adopted to exclude the disease.

A New Prophylactic Remedy against Diphtheria.—E. VON BEHRING (*Deutsch med. Woch.*, 1913, xxxix, 873) reports his recent studies in the prevention of diphtheria by the use of a mixture of diphtheria toxin and antitoxin. The mixture has been employed in a large series of animal experiments and finally in man by the von Behring colleagues in the Marburg clinics. The mixture of toxin and antitoxin employed is one which is practically non-toxic to guinea-pigs. It is found, however, that this mixture is not inert in all animals. Repeated doses of it may kill an ape, so that the toxin cannot be said

to be neutralized. Toxin and antitoxin given in this proportion, however, is practically non-toxic to man. By injecting small quantities of this preparation a high degree of active immunity may be conferred on patients. It is estimated that sufficient antitoxin units will remain in the blood to confer immunity for a period of two years. It is found, moreover, by obtaining serum from an actively immunized patient and injecting it into a second patient, that the injection of this homologous serum produces an immunity which greatly outlasts that produced by heterologous sera. The remedy is not given out yet for general use. Behring is collecting data from a few clinics. Before administering the serum, the presence or absence of antitoxin in the patient's blood is determined; if present, the quantity of antitoxin is estimated. The presence or absence of diphtheria bacilli in the respiratory passages is also determined. Then after the remedy is given, Behring requires that the quantity of antitoxin units in the patient's blood be determined at intervals for a long period of time and also that throat cultures be examined frequently for diphtheria bacilli. In this way, he plans to obtain exact information as to dosage, reaction, the amount of antitoxin produced in the human blood, and the duration of the protective reaction. When sufficient material has been collected, a further report will be made.

New Preparations and New Principles for the Treatment of Trypanosomiasis.—W. KOLLE, O. HARTOCH, M. ROTHERMUNDT and W. SCHÜRMAN (*Deutsch med. Woch.*, 1913, xxxix, 825) report the results of important studies of the chemotheraphy of experimental trypanosome infections. The observations were carried out largely upon mice. The organisms used were the trypanosomes of the sleeping sickness, nagana, and dourine. The authors have found that it is possible to cure experimental trypanosome infections of mice with a single intramuscular injection of metallic antimony as well as with various water-insoluble organic and inorganic preparations of antimony, provided the antimony is in the trivalent form. After the injection of metallic antimony and numerous preparations of antimony, however, the mice died of chronic antimony poisoning. Certain antimony compounds nevertheless, are relatively non-toxic when administered intra-muscularly. Of these a 30 per cent. oil emulsion of trioxide of antimony, which the authors designate "trixidin" for the sake of brevity, has proved the most efficient. It is the most active preparation examined, when given intramuscularly. It is found that $\frac{1}{100}$ of the fatal dose is sufficient to cure infections in mice. No evidence of antimony poisoning followed its use. Through one or two intramuscular non-toxic doses of trixidin, sterilization of infected mice is accomplished in 100 per cent. of cases. In its therapeutic index (1 to 100) and in its effectiveness it far surpasses previously studied preparations of antimony. The authors believe it will prove equally non-toxic and useful in the treatment of trypanosomiasis in man. The pentavalent antimony compounds are not only weak pharmacologically and toxicologically, but they are also without any marked therapeutic effect in trypanosome infections. Next the authors tried to find a method of employing trivalent compounds which are too toxic to be safe when given intramuscularly, but which are none the less highly active

against the trypanosomes. They have discovered that these preparations when incorporated in an ointment may be used as an inunction with very good results. Thus, metallic antimony and certain insoluble compounds in the form of a salve may cure infections of mice, rats, guinea-pigs, rabbits, and monkeys in about 66 per cent. of cases without the slightest evidence of toxic action. In contra-distinction to therapia magna sterilisans which on account of the large quantity of soluble drug quickly thrown into the circulation is dangerous and which must be repeated at intervals as the experience with salvarsan has shown, the authors designate their antimony treatment, therapia mite curans.

Avian Tuberculosis in Man.—E. LOEWENSTEIN (*Wein. klin. Woch.*, 1913, xxvi, 785) reports observations on three new cases of human infection with avian tubercle bacilli. He summarizes his studies as follows: The occurrence of avian tuberculosis in man is probably much commoner than is generally supposed. The cases are characteristic both bacteriologically and clinically. In all cases in which one finds acid fast bacilli, which are non-pathogenic for guinea-pigs, rabbits and chickens should be inoculated, and pure cultures of the organisms should be obtained. A simpler method of identification of the disease consists in the use of the skin test with avian tuberculin. Children infected only with avian tubercule bacilli do no react to human tuberculin but give a marked skin reaction with avian tuberculin. The clinical course in 2 cases of renal avian tuberculosis suggested benign septicemia with normal morning temperature and an evening rise (to 38.8° C.). The temperature in these 2 cases was uninfluenced by antipyretics; though the disease had lasted two years, the general condition of the patients was good. The local signs were not marked. Both of these patients who reacted only to avian tuberculin were treated with this substance and have remained free from symptoms for a year. The infection may result from eating the eggs of tuberculous hens, as the eggs may contain large numbers of tubercle bacilli. In experimentally infected eggs, soft boiled, the tubercule bacilli were uninjured; from two hard boiled eggs, viable bacilli were recovered.

Lymphocytosis in Chronic Polyarthritis.—F. GUDZENT (*Deutsch med. Woch.*, 1913, xxxix, 887) has made a careful study of the blood picture in 100 cases of chronic polyarthritis. The red cells and hemoglobin showed no noteworthy alterations. The leukocytes were normal in total number. Differential count showed a lymphocytosis in a majority of the cases. It amounted to 25 to 30 per cent. in 19 cases; 30 to 40 per cent. in 42 cases; 40 to 50 per cent. in 24 cases; 50 per cent. in 8 cases. In 9 cases the blood picture was normal. The lymphocytosis was present regardless of the stage of the disease. In view of the uncertainty of the etiology of this symptom complex, it is impossible to speculate as to the cause of the change in the leukocytic formula, but the association of increase in lymphocytes in chronic polyarthritis must be borne in mind when lymphocytosis is discovered.

SURGERY

UNDER THE CHARGE OF

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Three Cases with Large Calculi Which were Absolutely Latent.—PILLET (*Jour. D'Urolog.*, 1913, iii, 763) reports three very interesting cases with large renal calculi, all having an absolutely latent course. The first patient, aged thirty-six years, had had urinary treatment for several months and both ureters had been explored. A radiograph showed multiple large renal calculi, but the patient refused operation. The second patient, aged thirty-five years, had suffered since 1910 from burning urination. Each evening on returning from work, his urine was red and turbid, and slightly purulent. He urinated about every three hours, day and night. The radiograph revealed a large, coral-formed stone, 11 cm. long and 6 cm. wide, with prolongations into the calyces. The kidney was absolutely painless, because completely destroyed. The third patient, aged forty-three years, was operated on in 1909 by Pillet, for three calculi of the left kidney. This operation was followed by the expulsion of two small ureteral calculi after ureteral catheterization. In this case a friction sound had been obtained, by the use of the ureteral catheter, during stethoscopic auscultation of the abdomen. This patient, at the present time, presents in his opposite kidney, three calculi, clearly visible in the radiograph. One calculus is of the size of a hen's egg. Each of the other two are about as large as a hazel nut. The patient refuses to be operated on. A voluminous pyonephrosis has been developing for some years. It extends from the thoracic border to the pubis in the median line. One of the calculi can be felt distinctly under the skin by simple palpation. The patient does not suffer and having refused operation up to the present time, Pillet considers that it is no contra-indicated because of the degree of cachexia present.

Abscess of the Liver at the Haiphong Hospital.—SAMBRUC (*Archiv. gén. d. Chir.*, 1913, vii, 641) reports a study of 100 cases of suppurative hepatitis, collected from the Haiphong Hospital, during a period of thirteen years, with particular reference to their interesting clinical features. Abscess of the liver at Tonkin, is nearly always of dysenteric origin. The dysentery, however, is often unrecognized, either because it passes unperceived or it is in an abnormal form (intestinal amebiasis in diarrheic form). The most frequent site of the abscess is in the

antero-superior portion of the right lobe (corresponding to the seventh, eighth, and ninth intercostal spaces, between the mammary and mid-axillary lines). It is four times less frequent in the left lobe. Those of the quadrate and spigelian lobes are very rare and never isolated. Multiple abscesses were observed in the proportion of 40 per cent. In 15 per cent. they were located, at least partially, along the inferior surface of the organ. Migration into neighboring organs, are usually, followed by death, unless the abscess is evacuated by vomiting, which is followed by cure in 50 per cent. of the cases. Spontaneous evacuation into the intestine, is fatal in 75 per cent. of the cases. The diagnosis of hepatic abscess is often very difficult. Some of the cases are atypical, simulating a thoracic lesion (pleurisy, tuberculosis), and abdominal lesion (appendicitis), or it evolves like a general infection (typhoid fever). There is no pathognomonic sign. The more characteristic symptoms may be missing, such as the hepatic pain and enlargement. The frequent existence of congestion of the liver, in the evolution of a dysentery, makes the errors in diagnosis much more frequent. One should suspect an abscess of the liver in all patients presenting a high afternoon temperature, of uncertain origin. Exploratory puncture alone, an inoffensive but often efficacious operation, can confirm the diagnosis. The diagnosis of multiple abscesses, is impossible to establish *a priori*. It is only by the evolution of the disease, after a first operation, that one can justly suspect the existence of other foci. In cases of probable abscess of the inferior portion of the liver, exploratory laparotomy is a logical operation. Juxta-phrenic abscesses are often unrecognized, because the exploratory punctures are made too low. The prognosis is severe, because of the extreme frequency of multiple abscesses. Among the postoperative complications, there is one that is often overlooked, the pleural effusion which, even when only small, is likely to cause death.

Histological Examination of the Gastric Mucosa in Gastric Ulcer and Carcinoma.—HEYROVSKY (*Deut. Zschr. f. Chir.*, 1913, cxxii, 359) says that the advance of modern pathological histology, has been due largely to the knowledge that only tissues preserved and fixed when living, give the true picture of the cell changes produced by disease. The gastric mucosa was removed with the lesion in a series of operations for gastric and duodenal ulcers and carcinomas, was fixed while in the living state, and was examined, histologically, with the following results: The material was obtained from 120 cases; of which 70 were cases of gastric ulcer, 7 duodenal ulcers, 15 carcinomas of ulcer origin, and 28 carcinomas without ulcer origin. A severe gastritis was found in 51.5 per cent. of the gastric ulcer cases, 42.9 per cent. of the duodenal ulcers, 66.6 per cent. of the ulcer carcinomas and 78.5 per cent. of the carcinomas without ulcer origin. The pathological changes in the mucus membrane, in all the above mentioned diseases, were almost the same and differed only gradually. In the cases of gastric ulcer associated with gastritis, no constant cause for the gastritis could be demonstrated. It was dependent in many cases on the duration of the gastric ulcer or the gastric stagnation. No unity could be shown between the histological picture of the fundus mucous membrane and the behavior of the gastric secretion. No characteristic changes could

be found in the fundus glands to account for the hypersecretion and hyperacidity. In the gastric ulcer cases, there were found frequent erosions of the gastric mucous membrane, which possibly play a role in the origin of the gastric ulcers. The ulcer patients who had, in addition, gastritis, after gastro-enterostomy, suffered more frequently from stomach troubles, than the patients with ulcer without gastritis, The histological examination of the gastric mucous membrane removed at operation, has great practical value with relation to the prognosis and the subsequent dietetic therapy.

A Contribution to the Functional Diagnosis of Gastric Disease by Means of Sahli's Method.—ZNOJEMSKY (*Deut. Zschr. f. Chir.*, 1913, cxxii, 393) calls attention to the fact that what we need most in connection with malignant disease of the stomach, is not improvement in technique, but the possibility of making an early diagnosis. He employed Sahli's method, with and without a modification of the test meal, in 700 cases and reports a series in which operation was performed. From his studies he concludes that a considerable diminution of the motility, secretion and acidity, and positive lactic acid, speak for carcinoma at the pylorus. Normal motility, diminished secretion and acidity, and positive lactic acid findings, speak for gastric carcinoma. Diminished motility, somewhat diminished secretion and acidity (lactic acid negative), speak for carcinoma at the pylorus on the base of an ulcer. Normal motility, somewhat diminished secretion and acidity (lactic acid negative), speak for gastric carcinoma on the base of an ulcer. Diminished motility, normal or diminished secretion, and hyperacidity, speak for pyloric ulcer. Normal motility, normal or diminished secretion, and hyperacidity, speak for gastric ulcer. Diminished motility, normal secertion and normal acidity, speak for gastroptosis. Normal or diminished motility, hypersecretion, almost normal acidity, speak for duodenal ulcer or ulcer behind the pylorus. Diminished motility, secretion and acidity, are usually a typical finding in cholelithiasis and Ren Migrans. Changing behavior of the secretion and acitity (now increased and now decreased), speak very often for pyloric spasm.

Radium in the Treatment of Malignant Disease.—KNOX (*Brit. Med Journ.*, December 7, 1913, 1196), who is director of the electro-therapeutic department of the Cancer Hospital, Brompton, England, says that in all cases of early cancer the operative method is undoubtedly the best; it is quicker, safer, and offers the best prospect of cure. Radium is a useful adjunct to the treatment of all cases, first as a prophylactic after operation and, failing operation, the next best method we possess. It must, however, be stated that *x*-rays are in selected cases quite as useful as radium. In patients who refuse operation, or are for other reasons not suitable for operation, radium is a useful remedy. In inoperable cases radium may help to render the case operable; and failing that is undoubtedly useful as a palliative measure.

THERAPEUTICS

UNDER THE CHARGE OF

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Clinical Effects of "Natural" and "Synthetic" Sodium Salicylate.—HEWLETT (*Jour. Amer. Med. Assoc.*, 1913, lxi, 319) in an endeavor to ascertain the merits of the claim that the sodium salicylate prepared from natural oils is inferior as a therapeutic agent to the sodium salicylate prepared by synthetic methods, obtained data by the coöperation of a number of clinicians of recognized standing. They were asked to use and to note the effects of test powders of sodium salicylate without knowning the sources, natural or synthetic, of the individual powders. The result of the coöperative investigation as to the relative therapeutic value of sodium salicylate derived from natural sources and of sodium salicylate prepared by synthetic methods shows no essential differences between the two. This was demonstrated not only by the opinions of those investigators who attempted to classify the effects of their powders but also by a study of all the reports submitted. The slight variations in one direction or the other as shown by the figures are such as one expects in any set of statistics. Indeed, the statistical variations in these figures are surprisingly small. Allowing, therefore, for statistical error, one must conclude that natural and synthetic sodium salicylate are indistinguishable so far as their therapeutic and toxic effects on patients are concerned.

The Therapeutic Use of Benzol.—KIRALYFI (*Wien. klin. Woch.*, 1913, xxvi, 1062) writes from the clinic of Koranyi, who was the first to recommend benzol for the treatment of leukemia. Kiralyfi warns that in the future greater caution is necessary with regard to the dosage of benzol. He believes that it is advisable to discontinue the remedy as soon as the number of the leukocytes begins to decline. In any case the administration of benzol should be immediately stopped when the leukocyte count has reached 25,000 or 20,000. This precaution is necessary because the diminution of the leukocytes continues for some time after the withdrawal of the remedy. Kiralyfi quotes Neumann who reported a case where the continued use of benzol seemed to cause a rapid diminution of the leukocytes to as low as 200 per cubic millimeter associated with severe and incontrollable epitaxis, the patient dying thirty-nine days after discontinuing the benzol treatment. Kiralyfi has had a similar case in which the remedy at first seemed to have a specific action against the disease, the patient feeling entirely well and the blood picture remarkably improved. The benzol treatment was discontinued but the leukocytes continued to diminish until the count was 2800. Severe epistaxis then occurred and lasted for seven days. Various local and general measures were

of little avail in controlling the hemorrhage, and finally the patient died twenty-two days after the withdrawal of the remedy. The leukocytes then were 460 per c.c., no myelocytes were found and only 3 per cent. of myeloblasts. This case had been regarded as a brilliant example of the curative action of the benzol treatment but Kiralyfi considers that the continued action of the benzol was responsible for the uncontrollable hemorrhage and final fatal result. Kiralyfi says that the benzol treatment has been tried in other affections than luekemia, mentioning various enlargements of the lymph nodes without increase of the leukocytes, the pseudoleukemias, and also polycythemia. Benzol seems to have the same effect in reducing enlarged lymph nodes as Röntgen-ray treatment, but the improvement is only temporary. Kiralyfi says that in true pseudoleukemia benzol has a marked and almost certain action upon the disease. He does not believe that nephritis is aggravated by benzol therapy, but, often, according to his experience, is definitely benefited.

The Vaccine Treatment of Typhoid Fever.—WALTERS (*Med. Record*, 1913, lxxxiv, 518) reports a total of 158 cases of typhoid treated by vaccines. These cases were in all stages of the disease and in the entire number there have been 17 deaths, a percentage mortality of 11. Among these fatal cases, Walters says there were 8 cases where for one reason or another but one dose of vaccine was given, and that when the patients were moribund or *in extremis*. Excluding these 8 cases and 2 others that died of complicating diseases, there has been a total of 7 deaths in the remaining 148 cases, or a percentage mortality of 4.7 among those where the treatment may be said to have had a fair trial. During this time a parallel series of 100 cases not receiving vaccines has been observed, and here there have been 13 deaths or a mortality of 13 per cent. Walters collected a series of 1120 cases treated by different observers and believes that results thus obtained are more suitable for statistical purposes. In this series of 1120 cases, there was a total of 67 deaths. Excluding certain of the deaths upon grounds similar to his own series of cases, the mortality percentage in the entire series was 5. The percentage of relapses was also much reduced, being 6 per cent. as compared with the 15, 20, or 25 per cent. usually reported. From his personal experiences and the statistics of others, Walters summarizes certain things he has learned, and believes that certain measures he has used can be improved upon. He says that the best results have been attained by preparing vaccine from an old, non-virulent culture which has been subcultured for years in connection with the Widal tests. A new culture is made from this and incubated for twelve hours. In comparing his dose with that of others, it seems probable that his may be increased to 100,000,000, 200,000,000, or possibly 500,000,000. An early diagnosis is most important; this can often be first made by blood culture, days before the Widal reaction appears. The vaccines, when properly used by an immunizator will not harm in any stage of the disease, or in a relapse; but the earlier they are used, the greater the prospect of benefit. A safe rule to remember is that the more severe the case, the smaller should be the dose. The interval between doses is variable. A dose or two after the temperature has reached normal will render relapses less frequent.

PEDIATRICS

UNDER THE CHARGE OF

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Vulvovaginitis in Young Children.—NATHANIEL BARNETT (*Archiv. Pediatrics*, 1913, xxx, 650) gives a report of studies in a special clinic for this class of cases. The spread of the disease is favored in hospitals where individual cases are not isolated and in schools where children use a common toilet. Crowding of children and adults in small homes of the poor also favors its spread. Out of 50 cases studied, 14 contracted the disease from the mother or sister who had a vaginal discharge, and with whom the patient slept. Chronicity and resistance to treatment are characteristic of this condition. The average duration was eight and a half months, the largest record of persistence of the disease was six years. The external appearance of the hymen may be normal but pus is usually found behind it. The cervix is deeply congested and pus exudes from the orifice. Superficial ulcerations are often seen on the cervical lips. A urethral speculum is used to explore the vagina. The complications in this series were arthritis of shoulder and wrist, chronic general peritonitis, pelvic peritonitis, and painful heel. The treatment consisted of irrigations of potassium permanganate 1 to 1000; bichloride of mercury 1 to 4000; Lugol's solution, 1 to 500; instillations of silver nitrate 0.25 per cent. and argyrol, 10 per cent. Vaccines which improved the complications, such as arthritis, had absolutely no effect on the local condition. After thoroughly testing various forms of treatment the following was adopted as the best. Daily vaginal douche of potassium permanganate solution 1 to 10,000; small daily doses of urotropin; use of the Kelly endoscope three times a week with direct application to the cervix and vaginal walls of Lugol's solution. Cases are considered cured if smears taken weekly are negative for three consecutive weeks. Out of 26 completed cases 7 were cured at the end of six months by irrigation alone. Out of 7 cases not responding to irrigations, 5 were cured in one month with the endoscope. Direct applications must be made to the deep point of infection. Cures can be obtained in a short time by treating the cervix with strong solutions. Prophylaxis is difficult. Sleeping alone, wearing a vulvar pad, individual sets of clothing, and keeping the hands away from the genitals are important points.

Radiographic Studies of the Gastro-intestinal Tract.—HENRY DWIGHT CHAFLIN (*Jour. Amer. Med. Assoc.*, 1913, lxi, 1419) reports his findings in a number of tests to determined the mobility and motility of the gastro-intestinal tract, by the rapidity with which a suspension of barium sulphate could travel from the stomach to the cecum and thence through the large intestine to the outlet of the body. The radiographs show the stomach almost free of barium within two hours after ingestion of the barium and most of the suspension in the small intestine.

In three hours and ten minutes the greater part of the barium was in the cecum, ascending colon, and hepatic flexure. In six hours the transverse colon also was filled up to the splenic flexure. In seven hours the rectum was well distended with barium and a considerable amount remained in the descending colon. In one radiograph a noticeable amount of barium is seen in the small intestine within twenty minutes of its being placed in the stomach. These tests were made on children of seven and eight months of age. Another series of cases was studied after a clysma of barium had been given to determine the form and location of the sigmoid flexure, distensibility of the colon, and patency of the ileocecal valve. The pictures were begun right after the injection. A great variability was observed in the mobility of the hepatic and splenic flexures and the transverse colon. Injected substances getting past the sigmoid flexure reach the cecum very quickly. In one case the ileocecal valve was patent. The sigmoid flexure varied remarkedly in form and situation. It seems to occupy greater space than has been supposed and may be twisted and doubled up in all directions during life and may occasionally reach as high as the transverse colon. This bears out the claim of Boas and Nothnagel that it is rarely if ever possible to pass a tube through this structure.

Relapsing Pneumonia in Children.—R. R. ARMSTRONG (*Brit. Jour. Child. Dis.*, 1913, x, 444) gives the division of acute pneumonia in children into lobar pneumonia which is least common; lobular which is most common, and that condition associated with suffocative or acute capillary bronchitis with peribronchial pneumonia. Delayed resolution occurs most frequently in the lobular type. Relapsing pneumonia generally gives well-defined clinical signs and Armstrong describes 4 cases which demonstrate this. These 4 cases each lasted thirteen weeks and began with fever and cough. The original lesion in the lung cleared up in these cases in five to seven days with a drop in temperature to normal or almost normal. Then, in from one to several days, the temperature would again rise and the signs of dyspnea, etc., again appear. On examination a fresh area or lobule was found to be affected. These relapses occurred as often as eight times during the course of the disease. Usually the upper portions of the lung were secondarily affected, even the apices; new areas of consolidation appearing with each relapse. In the earlier relapses the bouts of pyrexia were prolonged and the intervals of normal temperature short. As illness progresses, however, the bouts of pyrexia are short, the fever never rises very high and fresh areas of infiltration, if present, are difficult to define. The pneumococcus was obtained in pure culture from two of the cases, the other cases were undoubtedly due also to this infection. Vaccine treatment showed no definite results. Strumous changes noted in some of these cases are possibly due to pneumonic toxins and a diagnosis of tuberculosis should not be made in long-continued pneumonias without examination and absolute proof clinically. The similarity between some children with chronic pneumonia and cretins suggests that thyroid extract may at times assist in promoting resistance to infection from pneumococci.

OBSTETRICS

UNDER THE CHARGE OF

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Bacteriological Examination in Fever Occurring During Labor.—SACHS (*Zeitschr. f. Geburts. u. Gynäk.*, 1912, lxx, No. 1) has studied the occurrence of fever during labor from the standpoint of bacteriology. He finds that where hemolytic streptococci are present in the birth canal they may cause fever during labor, whether in pure culture or not. The temperature may rise rapidly, and apparently without other cause. Other sorts of bacteria produce fever after much longer labor. In these cases other complications, such as placenta prævia, the use of the tampon, or the presence of predisposing blood clot, are of importance. The so-called streptococcus viridans seems to have little effect in producing fever during labor. The Bacillus coli communis produces fever rapidly, but, when in pure culture and in labors not unduly protracted, they produce no dangerous infection. Staphylococci are of very little importance in the production of fever during labor. In rare cases they become so virulent as to produce an effect. In cases that are not in the hospital, and in emergency births, such as those sometimes occurring in railway stations, in shops, or upon the street, if repeated examinations were made, bacteria which ordinarily are not pathogenic, may produce fever during labor. Thus, in one case the Streptococcus viridans was present in a case complicated by transverse position and rupture of the uterus. In another case, infection with the colon bacillus developed in transverse position, which made necessary the amputation of the fetal arm.

As regards the character of the fever and the condition of the pulse, streptococcus infection produces a rapid pulse—usually to 100 and often above. In other varieties of infection the pulse often remains below 100. In general, it may be said that with a temperature of 103.5° to 104°, and pulse above 100, that streptococcus infection is undoubtedly present, and with a low pulse and temperature the infection is from some other less virulent bacillus. As regards infection during labor, and its result in the puerperal period, the duration of labor accompanied by infection does not have great influence, nor does the causal element in producing fever during labor enable one to judge concerning what will happen in the puerperal period. Should labor be greatly prolonged, with fever, the puerperal period will undoubtedly be complicated. The occurrence of decomposition with foul lochia and with chills, does not necessarily indicate severe complications after birth. When we consider the variety of bacteria which produce fever during labor and its influence upon the puerperal period, we find that the morbidity during the puerperal period in streptococcus infection of the hemolytic variety, is three times as great as with any other. Where the puerperal period is greatly complicated by fever and other varieties

of organisms are present, there has been some other element to account for the complication. The presence of a pure culture is of significance in streptococci only. There is, however, a great influence exerted upon the puerperal period in the method of delivery. The more extensive and prolonged the interference, the greater is the development of fever and other complications in the puerperal period. The more virulent the infection during labor, the more imperative is it to avoid wounding the patient's tissues during labor. Spontaneous labor is to be secured, if possible, in this case.

Labor Complicated by a Gauze Pad Left in Douglas' Pouch.—Doleris (*Bull. de la Soc. d'Obstét. de Paris*, July, 1912) reports the case of a patient upon whom section was performed following pelvic inflammation. Pregnancy afterward developed, and, upon examination, the cervix was high up behind the symphysis and the vagina blocked with a bulky mass which filled Douglas' pouch. This resembled in feeling a universally adherent dermoid cyst. Labor came on without progress, and delivery was effected by Cesarean section. After the uterus had been closed, a deposit of organized lymph was found behind the uterus covering the pelvic cavity, and resembling a fold of peritoneum. When this was carefully opened, thick pus exuded freely. This membrane was carefully incised and a mass lying beneath it removed, which proved to be a guaze pad that had been in the pelvis over a year and a half. In view of the infection present, hysterectomy was performed, drainage inserted, and serum was administered with stimulants. During the second day there was distention, with urticaria, and later the right parotid gland inflamed, but this complication disappeared within twenty-four hours. The patient gradually recovered.

Arterio-venous Transfusion in Puerperal Hemorrhage.—Oui (*Annal. d. Gin. et l'Obstet.*, November, 1912) has frequently used intravenous saline transfusion in postpartum hemorrhage, and usually with satisfactory results. In the case of a young multipara, pregnancy was complicated by infection of the right kidney. Just before term the patient had hemorrhage, and, on examination, the membranes were found ruptured, the head engaged, but the placenta separating, with internal hemorrhage. The patient was delivered with difficulty with very copious bleeding, as the placenta had become completely detached. Other methods failing, and the patient becoming unconscious, it was determined to try arterio-venous transfusion. Accordingly, the husband's right radial artery was anastomosed with the patient's right median cephalic vein. Local anesthesia was employed for the husband. The transfusion was continued for nearly an hour, with evident improvement in the wife and without a sign of syncope on the part of the husband. The anastomosed vein and artery were resected a little above the line of suture, and no contraction or coagulation could be detected. The patient's improvement was immediate, and her convalescence was prolonged by the pyelonephritis. She finally, however, made a complete recovery, which is ascribed to the direct transfusion.

GYNECOLOGY

UNDER THE CHARGE OF

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Conservative Surgery in Genital Tuberculosis.—PATEK AND OLIVIER (*Rev. de Gyn.* 1913, xxi, 25), report the results of the recent examination of 33 patients upon whom some form of conservative operation had been performed since 1900 for tuberculosis of the internal genitalia. They used the vaginal route in only four instances, and think it should be discarded altogether, as it does not give the clear view of the affected area which is essential to the proper performance of any type of conservative operation. Simple laparatomy, without the removal of anything, as has been advocated by some authors, they also condemn, believing that no good is accomplished by such operations, except possibly in a very few far advanced cases, where anything more radical is out of the question at the time. In such instances, a simple laparotomy may occasionally lead to a temporary amelioration of conditions, and thus permit of a second, more radical procedure. Operations in which the uterus is allowed to remain, although both tubes and ovaries are removed, are likewise considered unjustifiable; such a uterus is useless, and although it may appear perfectly healthy, it may subsequently become tuberculous and require removal, as in one of Patek and Olivier's series. In rare instances, however, the uterus may be so densely surrounded by tuberculous exudate that to remove it would add tremendously to the shock of the operation; in these cases, they consider it justifiable to leave the uterus, even if both adnexa have been removed. Most of Patek and Olivier's cases in which true conservatism was practiced have done exceedingly well, and have regained excellent health, though a few continue to suffer from abdominal pains, and on examination are found to have a tender pelvic exudate. One woman, from whom everything was removed except one ovary, underwent all the symptoms of the artificial menopause. In only one instance did pregnancy subsequently occur; the sterilizing effect of the tuberculous process is so great that such cases must always remain the exception, so that the possibility of preserving this function does not carry much weight in determining in any given case the type of operation. In questioning a large number of women upon whom the *radical* operation had been performed for genital tuberculosis, one of the authors has brought out the interesting point that such patients complain very little of the symptoms commonly associated with the artificial menopause, this probably being due to a slow reduction which has taken place in the ovarian activity as a result of the tuberculous infection, thus gradually accustoming the organism, as it were, to its absence. In view of this fact, and of the slight chance in most instances of a subsequent pregnancy, Patek and Olivier believe that conservatism in dealing with genital

tuberculosis is indicated more on sentimental than practical grounds; they do consider it justifiable in young women, however, where the ovaries themselves are not found distinctly infected; where such is the case, only the truly *radical* operation (removal of uterus with both tubes and ovaries) can be depended upon to cure.

Tuberculous Pyosalpinx Perforated into the Bladder.—ISRAEL (*Deutsch. med. Woch.*, 1913, xxxix, 2295) reports a most unusual case of genito-urinary tuberculosis, occurring in a young girl, and presenting several features of interest from both the diagnostic and therapeutic standpoint. When the patient first consulted him, at the age of twenty-two years, she complained of failing health for the previous years, with increasing dysuria, night sweats, and feverish attacks. The urine was cloudy, contained pus, and on one examination tubercle bacilli, though on several subsequent examinations these could not be found. Cystoscopic examination showed a much inflamed bladder, with a tuberculous ulcer on the right side, and urine from each kidney, obtained by ureteral catheterization, produced tuberculosis in all inoculated animals; the same results were obtained upon a second examination. The case was therefore diagnosed as one of bilateral renal tuberculosis, unsuitable for operation, and sanatorium treatment advised. After eleven months of this the patient returned having gained 38 pounds, and presenting the appearance of perfect health. Cystoscopic examination again showed much inflammation, but no ulcer; palpation of both kidneys was absolutely negative. Israel's suspicions were now aroused as to the correctness of the former diagnosis, and a careful bimanual examination was made under ether, revealing an indefinite tumor mass in the neighborhood of the uterus, reaching to above the symphysis. Following this examination there was an intense febrile reaction lasting several days. A second ureteral catheterization was now undertaken with the greatest precautions to prevent any bladder urine from flowing out through the catheters; the urine obtained in this manner gave absolutely negative results in all injected animals, whereas that from the bladder uniformly caused death from tuberculosis. The true nature of the case was now clear; the kidneys were healthy, and the urine obtained from them at the first two ureteral catheterizations had been mixed with that from the infected bladder during the passage through it of the catheters, and had thus given the positive guinea-pig reactions. The mass felt was evidently a tuberculous focus communicating with the bladder, and intermittently discharging into it. A laparotomy confirmed this opinion; a tuberculous pyosalpinx was with great difficulty shelled out of a dense mass of pelvic adhesions, a distinct band, containing a lumen, being demonstrable between it and the bladder wall. Following the operation the urine gradually cleared up, and all symptoms disappeared rapidly, but tubercle bacilli remained for six months before entirely disappearing. The abdominal wound, however, gave much trouble, numerous fistulous tracts being formed, but after about seven months healing finally took place. Two years after operation the patient reports excellent health.

OTOLOGY

UNDER THE CHARGE OF

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Local Anesthesia of the Drum-head.—BLEGVAD (*Deutsch. med. Woch.*, xxviii, 1912) says that under normal conditions the drum-head is practically impermeable, because of the superimposed layers of pavement epithelium forming its outer coat, so that the admission of fluids from without to the deeper tissues is possible only through some solution of continuity of the dermoid coat. This fact has been availed of by Gray and Bouerius with good results, a removal of a limited area of the resistant tissues, either by incision or by erosion before application of the anesthetic solution having sufficed to effect a deadening of sensibility throughout the drum-head sufficient to permit of paracentesis, of multiple incisions, the removal of small polypi and other circumscribed operations, with only slight discomfort. To the character of the anesthetic, in both instances, Blegvad takes exception on account of their toxic properties, that of Gray containing analine oil to the extent of from 50 to 70 per cent., and of Bouerius phenol in addition to cocaine, and recommends, as a substitute, cocaine and salycilic acid in equal parts in double the quantity of absolute alcohol with the addition of a 1 per cent. adrenalin solution.

Angiosclerotic Otalgia.—Within a period of ten years STEIN (*Wien. klin. Woch.*, 1912, xxvi) had observed 246 cases diagnosticated as arteriosclerosis upon the basis of both the general and the aural examinations. Of this number 37 or 15 per cent. complained of discomfort or pain in the region of the ears, but so far as a demonstrable local cause for pain was concerned, the aural examination was, in all these cases, negative. The pain was usually directly localizable, in the depth of the ear, not infrequently in the external auditory canal, and sometimes in the mastoid region and the sensations, which were usually monaural, rarely binaural, were described as pressure, stretch-pricking or resembling a cramp, they were either continuous, with variations in intensity, or intermittent and were referred, by Stein, as the result of a series of observations of the general as well as the local manifestations, to arteriosclerotic changes in the bloodvessels distributed to the ear which, by decreasing or interrupting the blood supply evoked the painful sensations familiar in other regions. Good results were attained by the administration of diuretin in 0.5 gm doses from three to five times daily, continued for several weeks, in more than one-half of the cases so treated the pain was decreased and finally disappeared.

Effect of Auditory Stimuli upon the Cerebral Circulation.—In the case of a young man, aged seventeen years, who, as the result of operation following an extensive fracture of the skull, had a cranial

opening in the frontal temporal region 13 by 8 cm. in area, CASTELLAN (*Archiv. International*, 1913, xxxv, 1) had an opportunity to repeat the observations of Dogiel and, in a measure, confirm them. Over the greater part of the bony defective space the skin of the scalp was in contact with the dura and partly adherent, rendering the diffused pulsation of the brain, synchronous with the radial pulse, both tangible and visible. In the right ear the middle ear was apparently normal, but the hearing was entirely wanting while the left ear heard normally. By attachment to the skin of the surgically created cranial foramen of a manometric capsule with a kymograph it was possible to still further observe, and to record, the cerebral pulsation in response to the acoustic stimulation of the left ear by means of tuning-fork tones applied close to the auricle. In response to the deeper-toned forks C2, C1, and C, the cerebral pulse increased in frequency with a slight decrease in the primary and an increase in the secondary impulse, indicating a decrease in arterial tension. Tones of medium and high-pitched forks were accompanied by a slight, but definite diminution in frequence, a marked elevation of the recorded curve, consonant with the increased blood pressure, and either a disappearance, or a marked decrease, of the secondary impulse.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Changes Occurring in the Voluntary Muscles in General Diseases.—JEWESBURY and TOPLEY (*Jour. Path. and Bact.*, 1913, xvii, No. 4) have conducted some interesting experiments dealing with the state of the muscles in certain so-called general diseases. In wasting diseases they find various degrees and kinds of histological change which do not seem closely related to the degree of wasting present, but which seem rather to be the result of intercurrent inflammation or toxemia. In acute general diseases, such as pneumonia, septicemia, diphtheria, eclampsia, etc., the changes are usually of the nature of hyaline or granular modification of the muscle cell and occasional fatty degeneration. In disorders of carbohydrate metabolism there is a very marked increase in the amount of interstitial fat. They found a small collection of fat droplets in the neighborhood of the nuclei frequently in advanced life, rarely in children, and very rarely in animals. The pathological significance of this fat Jewesbury and Topley were unable to determine. The most interesting point of their observations is that the incidence of fatty degeneration has been much over-stated; nevertheless, they found it very marked in diphtheria and phosphorus

poisoning, in infective purpura, and in severe anemia. Glycogen was sought for in a large variety of diseases, but it was found in considerable amount only in diabetes. Amyloid change was not found in the series, although 12 cases were examined whose nature would render the presence of amyloid in the muscle a possibility.

Blood Platelets in Blood Repair.—Le Sourd and Pagniez (*Jour. de Phys. et Path. Gén.*, 1912, xiv, No. 6) have made experiments with a view to determining the part played by the platelets in repair of blood loss, and find that they can alter the platelet content without necessarily changing the red corpuscle content of the blood. The outburst of hematoblasts following upon an excessive bleeding can be prevented without at the same time preventing the repair of the blood loss; so that these two processes which appear to be very intimately connected can actually be dissociated. That the platelets and red blood cells are not intimately associated, is also seen in cases of purpura hemorrhagica, where the number of platelets may sink very greatly, or may even sink to zero, while the red blood cells preserve their normal number. Nevertheless, in the majority of cases, numerical variations of the platelets do run somewhat parallel to that of the red cells, and the determination of a rapidly increasing platelet count determines a favorable degree of activity in the blood-forming organs; on the contrary, the progressive and permanent lowering of the platelet count coinciding as it does with the lowering of the red corpuscle count in pernicious anemia, is a further indication of the inactivity of blood-forming organs. Le Sourd and Pagniez consider that the previous statements of Achard and Aynoud were correct, when they considered the platelets as numerically variable, independent of the other elements of the blood.

An Improved Method for the Histological Study of the Arteries.—MacCordic (*Jour. Path. and Bact.*, 1913, xvii, No. 4) has devised an extremely useful method of studying arteriosclerotic and other arteries, without the preparation suffering from the contraction which usually occurs post mortem, and which is responsible for a histological picture actually much different from that obtained in an artery whose natural state is preserved after death. MacCordick has succeeded in permanently relaxing the artery by subjection to a solution of ammonium sulphocyanide. After removing a piece of artery from the body it is immersed in 20 per cent. solution of the above substance, then washed in normal saline, and to each end of the artery a small glass cannula with rubber tubing is attached. While remaining in saline solution, air is pumped in, and the presence of small branches is noticed by the escape of air bubbles; such branches may be readily ligated. The artery is next attached by means of these tubes to a pressure apparatus with a manometer, and Zenker's solution or 10 per cent. formalin is pumped into the artery, which meantime is immersed in a similar solution. By additional force, the tubes being clamped, the pressure of the solution inside the artery is raised to 150 mm. of mercury, although for normal arteries a pressure of 100 mm. answers the purpose. This pressure is kept up during twenty-four hours, at the end of which time the artery is permanently fixed. MacCordick's

diagrams indicate how perfectly the *intra vitam* state of the artery is preserved. Subsequent to fixation the tissues are treated in the usual way. While the suggestion for this piece of work arose in MacWilliams' publications, nevertheless the application of this usefully modified procedure to diseased arteries, seems to rest with MacCordick.

Factors in the Formation of Metastatic Tumors.—Tyzzer (*Jour. med. Research*, July, 1913, xxviii, No. 2, 309) experimented upon mice in which tumor metastases were developing, and draws the practical conclusion that manipulation of a tumor, even in its early stages, is apt to cause metastasis, and that handling and massage are more likely to cause metastases than is section of the primary mass: the deduction for the clinician is a simple one. Operation which includes section of the primary tumor does not increase the liability to secondary growth; secondaries grow more rapidly, however, after removal of a large mass of tumor tissue elsewhere (the so-called *athrepsia* of Ehrlich), as well as under improved physical conditions of the body. In the mice operated upon, Tyzzer had, by long observation, noted accurately the time of appearance of secondary growths, and if removal of the primary tumor was undertaken just prior to this time, secondaries did not arise. The period called "premetastatic" exists rather on account of the absence of the conditions necessary for dissemination than on account of any resistance inherent in the body. Manipulation of the primary tumor shortens the duration of this premetastatic period.

The Pathological Anatomy of Paratyphoid Fever.—Saltykow (*Virchow's Arch.*, 1913, Band ccx) collected 22 cases of this affection from literature, of which 14 showed implication of the lymphoid tissue, ulceration being present in 9. Without being in any sense typical, the lesions of paratyphoid are very similar to those of typhoid. In the latter disease, it is interesting to note that Purjesz and Perl (*Wien. klin. Woch.*, 1913, No. 40) found the characteristic bacilli, 4 times out of 7 patients, in the tongue-scrapings and upon the tonsils; in half of the *convalescent* patients examined, the bacilli were demonstrable at times varying from the fifth to the forty-seventh day after the active disease had subsided. The tongue gave positive results oftener than the tonsils.

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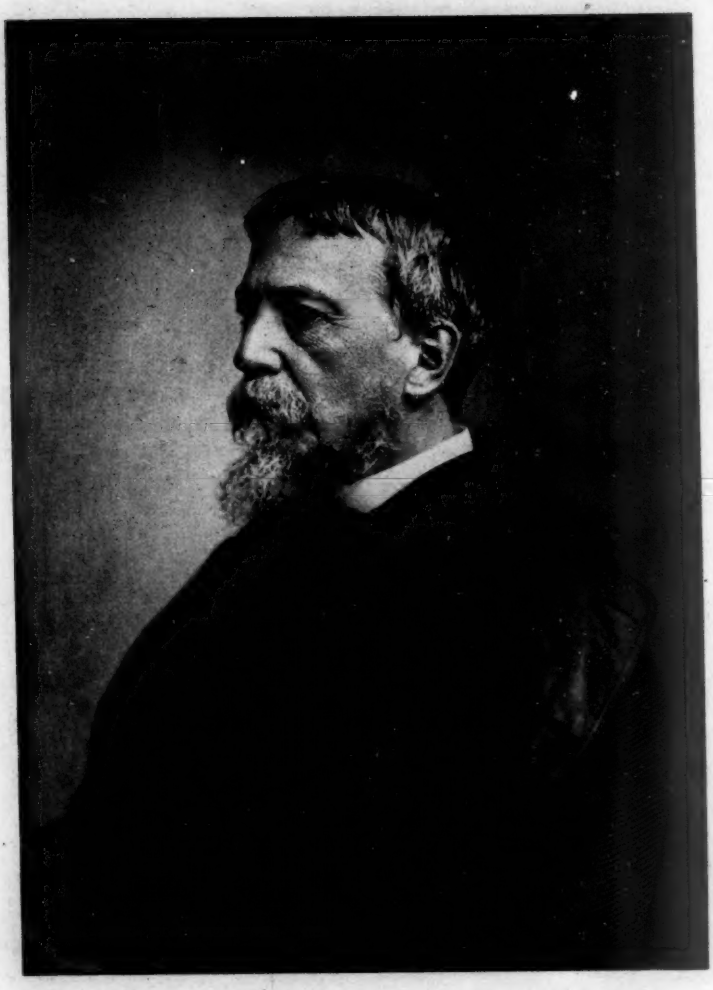

Weir Mitchell